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(54) Title: NITROGEN-CONTAINING HETEROCYCLYL SUBSTITUTED IMIDAZOQUINOLINES AND IMIDAZONAPHTHYRIDINES

(57) Abstract: Imidazoquinoline and imidazonaphthyridine compounds having a nitrogen-containing heterocyclyl substituent at the 5-, 6-, 7-, or 8-position, pharmaceutical compositions containing the compounds, intermediates, and methods of making and methods of use of these compounds as immunomodulators, for modulating cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases are disclosed.

NITROGEN-CONTAINING HETEROCYCLYL SUBSTITUTED IMIDAZOQUINOLINES AND IMIDAZONAPHTHYRIDINES

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority to U.S. Provisional Application Serial No. 60/579829, filed on June 15, 2004, which is incorporated herein by reference in its entirety.

BACKGROUND

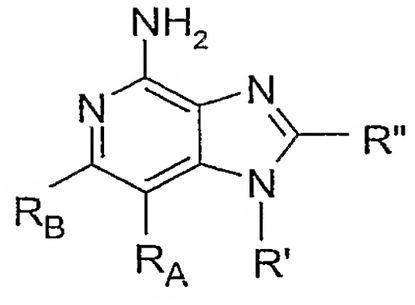
In the 1950's the 1*H*-imidazo[4,5-*c*]quinoline ring system was developed and 1-(6-568-quinolinyl)-2-methyl-1*H*-imidazo[4,5-*c*]quinoline was synthesized for possible use as an antimalarial agent. Subsequently, syntheses of various substituted 1*H*-imidazo[4,5-*c*] quinolines were reported. For example, 1-[2-(4-piperidyl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline was synthesized as a possible anticonvulsant and cardiovascular agent. Also, several 2-oxoimidazo[4,5-c]quinolines have been reported.

Certain 1*H*-imidazo[4,5-*c*]quinolin-4-amines and 1- and 2-substituted derivatives thereof were later found to be useful as antiviral agents, bronchodilators and immunomodulators. Subsequently, certain substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amine, quinolin-4-amine, tetrahydroquinolin-4-amine, naphthyridin-4-amine, and tetrahydronaphthyridin-4-amine compounds as well as certain analogous thiazolo and oxazolo compounds were synthesized and found to be useful as immune response modifiers, rendering them useful in the treatment of a variety of disorders.

There continues to be interest in and a need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other mechanisms.

SUMMARY OF THE INVENTION

It has now been found that certain nitrogen-containing heterocyclyl substituted imidazoquinoline and imidazonaphthyridine compounds modulate cytokine biosynthesis. Such compounds are of the following Formula I:



I

wherein R_A, R_B, R', and R" are as defined below; and pharmaceutically acceptable salts thereof.

The compounds of Formula I are useful, for example, as immune response modifiers (IRMs) due to their ability to modulate cytokine biosynthesis (e.g., induce or inhibit the biosynthesis or production of one or more cytokines) and otherwise modulate the immune response when administered to animals. Compounds can be tested, for example, using the test procedures described in the Examples Section. Compounds can be tested for induction of cytokine biosynthesis by incubating human PBMC in a culture with the compound(s) at a concentration range of 30 to 0.014 μM and analyzing for interferon (α) or tumor necrosis factor (α) in the culture supernatant. Compounds can be tested for inhibition of cytokine biosynthesis by incubating mouse macrophage cell line Raw 264.7 in a culture with the compound(s) at a single concentration of, for example, 5 μM and analyzing for tumor necrosis factor (α) in the culture supernatant. The ability to modulate cytokine biosynthesis, for example, induce the biosynthesis of one or more cytokines, makes the compounds useful in the treatment of a variety of conditions such as viral diseases and neoplastic diseases, that are responsive to such changes in the immune response.

The present invention further provides pharmaceutical compositions containing an effective amount of a compound of Formula I and methods of inducing cytokine biosynthesis in an animal, treating a viral infection and/or treating a neoplastic disease in an animal by administering an effective amount of a compound of Formula I to the animal.

In addition, methods of synthesizing compounds of Formula I and intermediates useful in the synthesis of these compounds are provided.

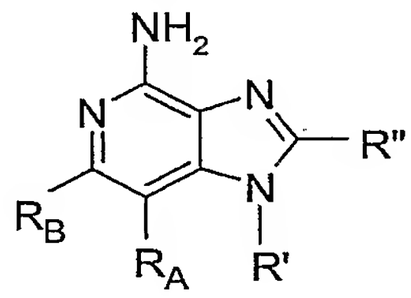
As used herein, "a", "an", "the", "at least one", and "one or more" are used interchangeably.

The terms "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the description, guidance is provided through lists of examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

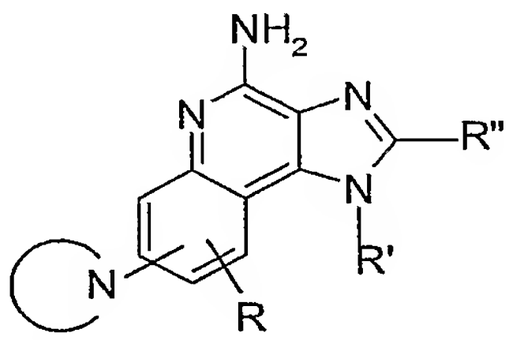
DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

The present invention provides compounds of the following Formula I:

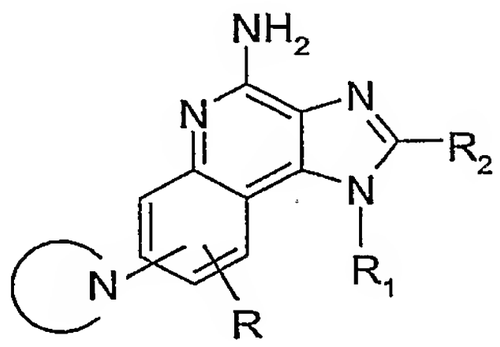


I

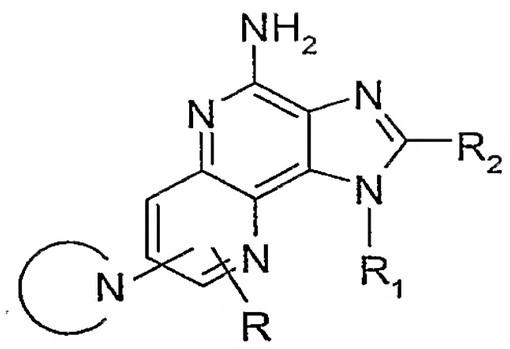
as well as more specific compounds of the following Formulas (II, IIa, III, and IV):



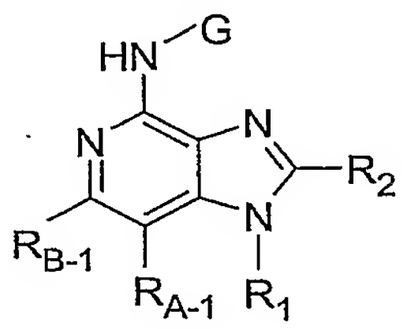
II



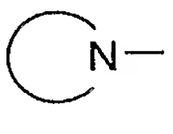
IIa



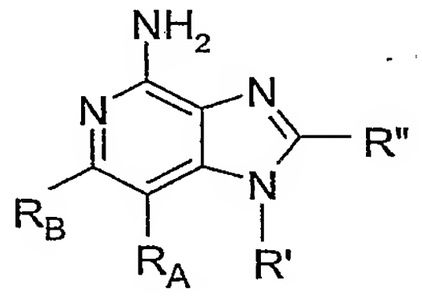
III



IV

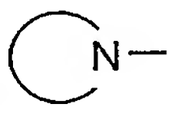
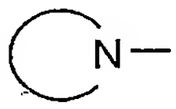
wherein R_A, R_B, R_{A-1}, R_{B-1}, R', R", R, R_1, R_2,  , and G are as defined below, and pharmaceutically acceptable salts thereof.

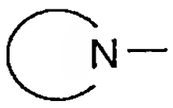
In one embodiment, the present invention provides a compound of Formula (I):



I

wherein:

R_A and R_B taken together form a fused benzene ring or fused pyridine ring wherein the benzene ring or pyridine ring is substituted by one  group, or substituted by one  group and one R group;

 is a heterocyclic ring system wherein the ring containing the nitrogen atom bonded to the imidazoquinoline or imidazonaphthyridine radical of the compound of Formula I is unsaturated or partially saturated, and wherein the heterocyclic ring system is mono-, bi-, or tricyclic, and can contain 4 to 14 ring atoms, up to 2 of which, in addition to the nitrogen atom bonded to the imidazoquinoline or imidazonaphthyridine radical, are optionally a heteroatom selected from N, O, and S, and wherein the heterocyclic ring

system is unsubstituted or substituted by one or more substituents selected from the group consisting of:

alkoxy,

alkylenedioxy,

hydroxy,

nitro,

oxo,

thioxo,

$-R_4$,

$-Y-R_4$,

$-X-Y-R_4$,

$=N-Q-R_4$,

=N-CN, and

=N-OH;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

$-O-C(O)-O-$,

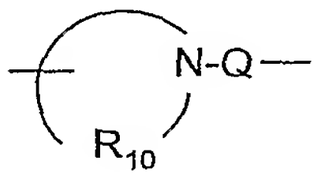
$-O-S(O)_2-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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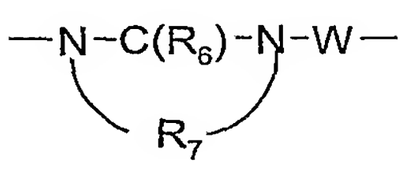

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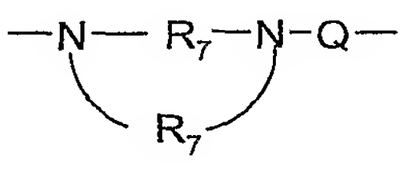

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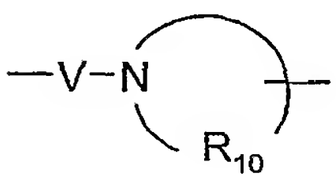

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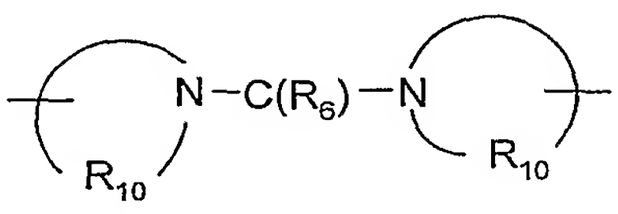


;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of a bond, $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

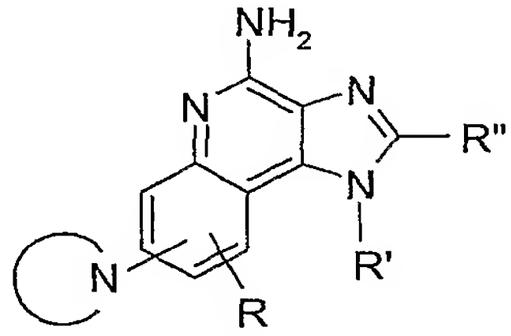
R_{10} is C_{3-8} alkylene;

R is selected from the group consisting of hydrogen, alkyl, alkoxy, trifluoromethyl, chloro, fluoro, and hydroxy; and

R' and R" are independently selected from the group consisting of hydrogen and non-interfering substituents;

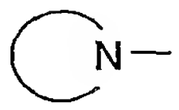
or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of Formula (II):



II

wherein:



is a heterocyclic ring system wherein the ring containing the nitrogen atom bonded to the imidazoquinoline radical of the compound of Formula II is unsaturated or partially saturated, and wherein the heterocyclic ring system is mono-, bi-, or tricyclic, and can contain 4 to 14 ring atoms, up to 2 of which, in addition to the nitrogen atom bonded to the imidazoquinoline radical, are optionally a heteroatom selected from N, O, and S, and wherein the heterocyclic ring system is unsubstituted or substituted by one or more substituents selected from the group consisting of:

alkoxy,

alkylenedioxy,

hydroxy,

nitro,

oxo,

thioxo,

$-R_4$,

$-Y-R_4$,

$-X-Y-R_4$,

=N-Q-R_4,

=N-CN, and

=N-OH;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

-O-C(O)-O-,

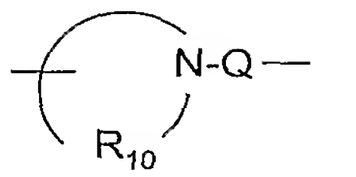
-O-$S(O)_2$-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

-$C(R_6)$-$N(OR_9)$-,



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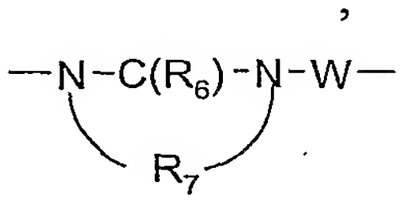

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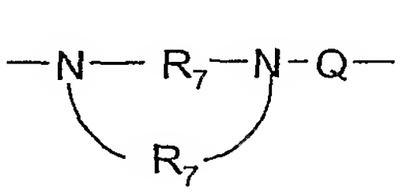

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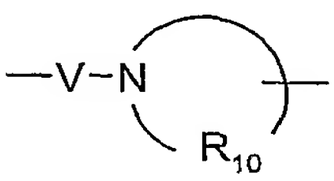

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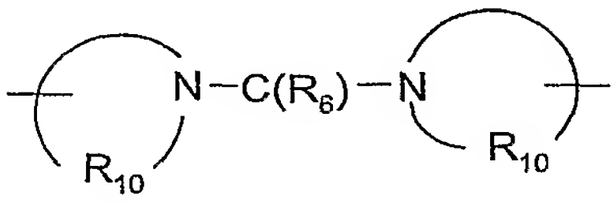


;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, and -$C(R_6)$-$N(OR_9)$-;

V is selected from the group consisting of a bond, -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

R is selected from the group consisting of hydrogen, alkyl, alkoxy, trifluoromethyl, chloro, fluoro, and hydroxy; and

R' and R" are independently selected from the group consisting of hydrogen and non-interfering substituents;

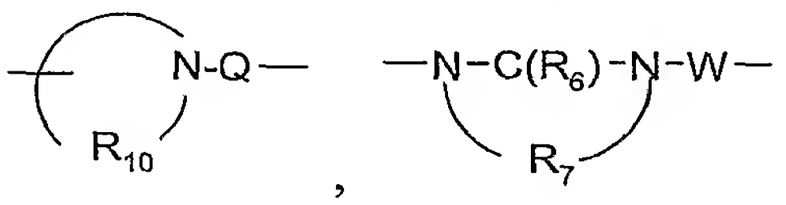
or a pharmaceutically acceptable salt thereof.

For certain embodiments of Formula II, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and

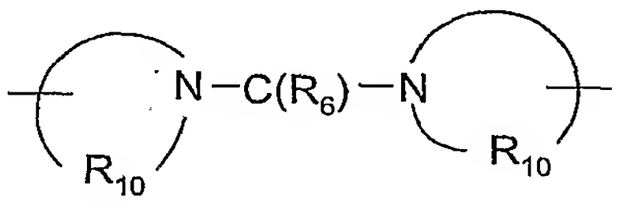
heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

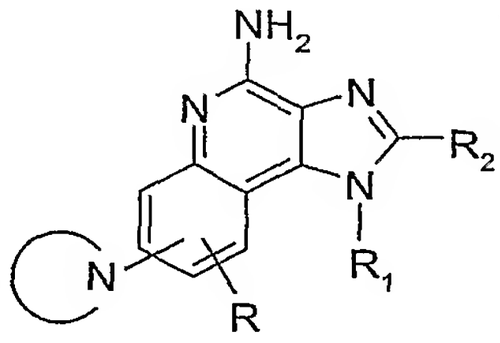
Y is selected from the group consisting of $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-O-S(O)_2-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$,



, and

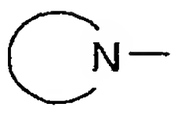


In another embodiment, the present invention provides a compound of Formula (IIa):



IIa

wherein:



is a heterocyclic ring system wherein the ring containing the nitrogen atom bonded to the imidazoquinoline radical of the compound of Formula I is unsaturated or partially saturated, and wherein the heterocyclic ring system is mono-, bi-, or tricyclic, and can contain 4 to 14 ring atoms, up to 2 of which, in addition to the nitrogen atom

bonded to the imidazoquinoline radical, are optionally a heteroatom selected from N, O, and S, and wherein the heterocyclic ring system is unsubstituted or substituted by one or more substituents selected from the group consisting of:

alkoxy,

alkylenedioxy,

hydroxy,

nitro,

oxo,

thioxo,

$-R_4$,

$-Y-R_4$,

$-X-Y-R_4$,

$=N-Q-R_4$,

=N-CN, and

=N-OH;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

$-O-C(O)-O-$,

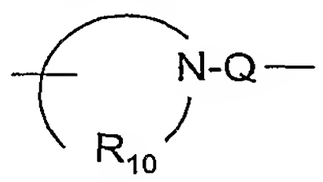
$-O-S(O)_2-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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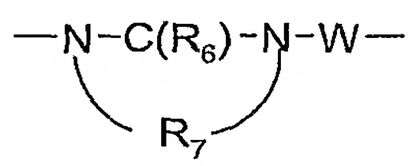

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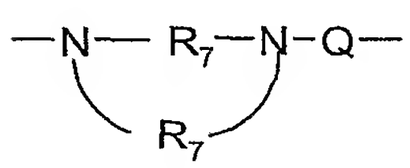

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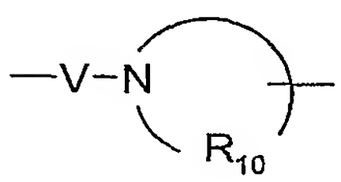
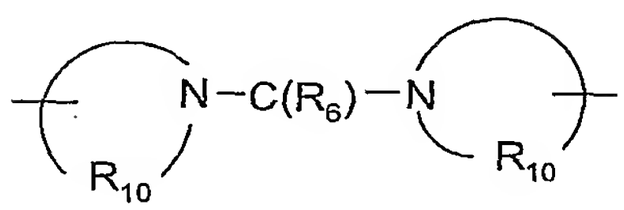


, and

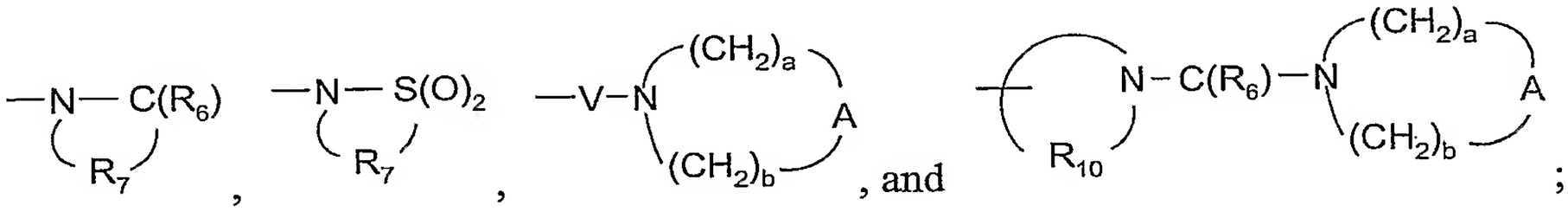


.

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl,

aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}$-, $-CH_2$-, and $-N(R_4)$-;

Q is selected from the group consisting of a bond, $-C(R_6)$-, $-C(R_6)-C(R_6)$-, $-S(O)_2$-, $-C(R_6)-N(R_8)-W$-, $-S(O)_2-N(R_8)$-, $-C(R_6)-O$-, and $-C(R_6)-N(OR_9)$-;

V is selected from the group consisting of a bond, $-C(R_6)$-, $-O-C(R_6)$-, $-N(R_8)-C(R_6)$-, and $-S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-;

each a and each b is independently an integer from 1 to 6 with the proviso that a + b in each ring is ≤ 7;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene; and

R is selected from the group consisting of hydrogen, alkyl, alkoxy, trifluoromethyl, chloro, fluoro, and hydroxy;

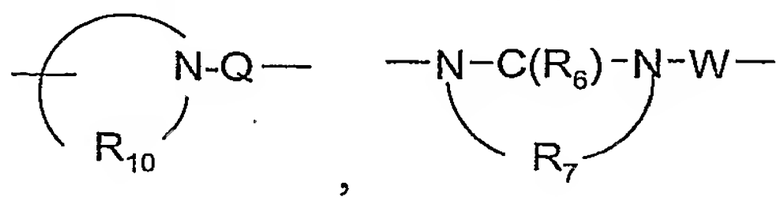
or a pharmaceutically acceptable salt thereof.

For certain embodiments of Formula IIa, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl,

haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

Y is selected from the group consisting of $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-O-S(O)_2-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$,



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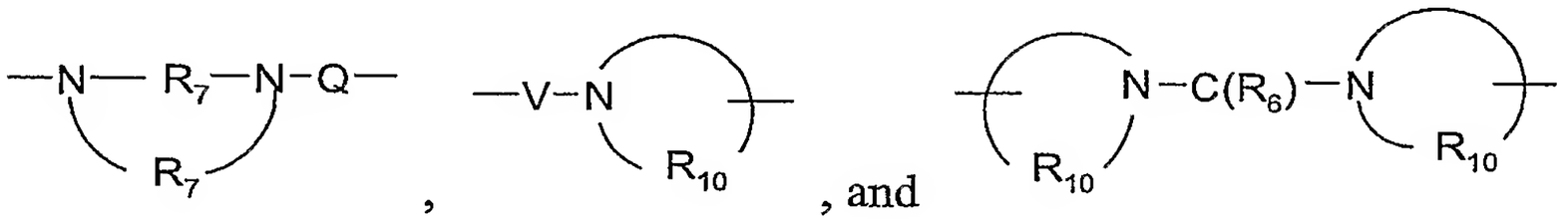
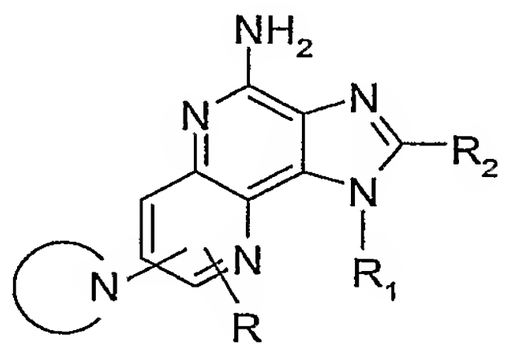


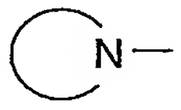
, , and .

In another embodiment, the present invention provides a compound of Formula (III):



III

wherein:



is a heterocyclic ring system wherein the ring containing the nitrogen atom bonded to the imidazonaphthyridine radical of the compound of Formula I is unsaturated or partially saturated, and wherein the heterocyclic ring system is mono-, bi-, or tricyclic, and can contain 4 to 14 ring atoms, up to 2 of which, in addition to the nitrogen atom bonded to the imidazonaphthyridine radical, are optionally a heteroatom selected from N, O, and S, and wherein the heterocyclic ring system is unsubstituted or substituted by one or more substituents selected from the group consisting of:

alkoxy,

alkylenedioxy,

hydroxy,

nitro,

oxo,

thioxo,

$-R_4$,

$-Y-R_4$,

$-X-Y-R_4$,

$=N-Q-R_4$,

=N-CN, and

=N-OH;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

-O-C(O)-O-,

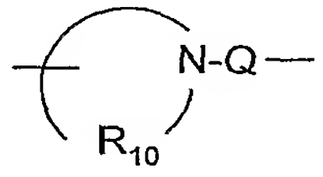
-O-S(O)$_2$-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

-C(R_6)-N(OR_9)-,



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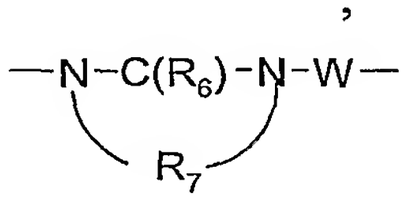

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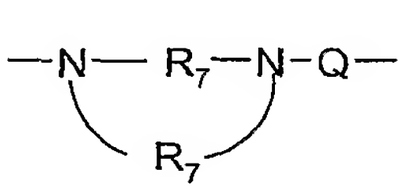

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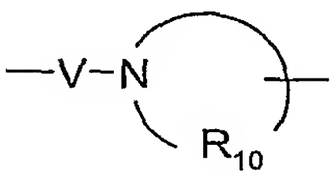

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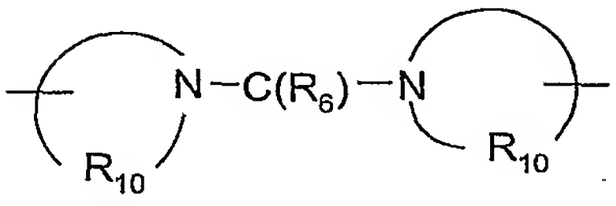
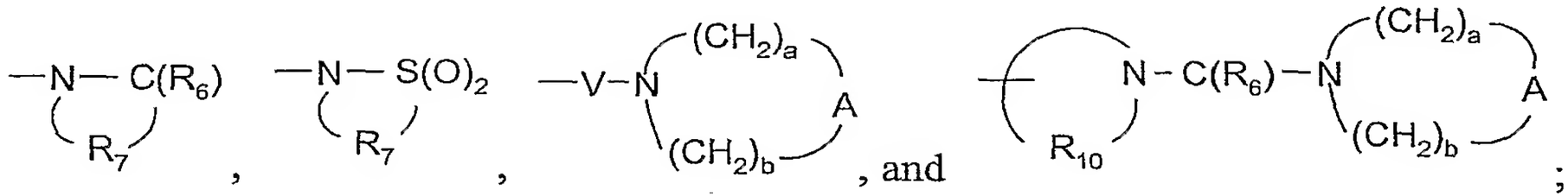


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

A is selected from the group consisting of -O-, -C(O)-, -$S(O)_{0-2}$-, -CH_2-, and -$N(R_4)$-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, and -$C(R_6)$-$N(OR_9)$-;

V is selected from the group consisting of a bond, -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-;

each a and each b is independently an integer from 1 to 6 with the proviso that a + b in each ring is ≤ 7;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

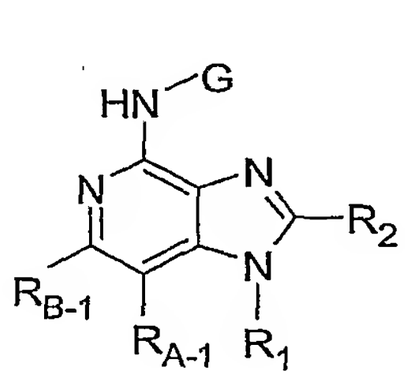
R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene; and

R is selected from the group consisting of hydrogen, alkyl, alkoxy, trifluoromethyl, chloro, fluoro, and hydroxy;

or a pharmaceutically acceptable salt thereof.

For certain embodiments, the present invention provides a compound (which is a prodrug) of the Formula (IV):



IV

wherein:

G is selected from the group consisting of:

-C(O)-R'",

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

-C(O)-O-R'",

-C(O)-N(R'"")R'",

-C(=NY')-R'",

-CH(OH)-C(O)-OY',

-CH(OC_{1-4} alkyl)Y_0,

-CH_2Y_1, and

-$CH(CH_3)Y_1$;

R'" and R"" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, and benzyl, each of which may be unsubstituted or substituted by one or more substitutents selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, arylC_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl, haloC_{1-4} alkylenyl, haloC_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2, with the proviso that R"" can also be hydrogen;

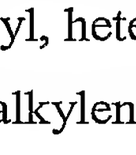
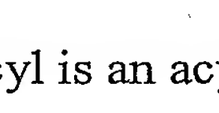
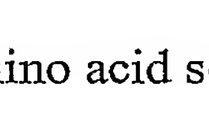
α-aminoacyl is an acyl group derived from an amino acid selected from the group consisting of racemic, D-,and L-amino acids;

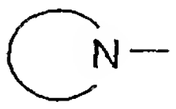
Y' is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl;

Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxyC_{1-6} alkylenyl, aminoC_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylaminoC_{1-4} alkylenyl, and di-*N,N*-C_{1-6} alkylaminoC_{1-4} alkylenyl;

Y_1 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl;

R_{A-1} and R_{B-1} taken together form a fused benzene ring or fused pyridine ring

wherein the fused pyridine ring is  wherein the highlighted bond indicates the position where the ring is fused, and wherein the benzene ring or pyridine ring is substituted by one  group, or substituted by one  group and one R group;

 is a heterocyclic ring system wherein the ring containing the nitrogen atom bonded to the imidazoquinoline radical of the compound of Formula I is unsaturated or partially saturated, and wherein the heterocyclic ring system is mono-, bi-, or tricyclic, and can contain 4 to 14 ring atoms, up to 2 of which, in addition to the nitrogen atom bonded to the imidazoquinoline radical, are optionally a heteroatom selected from N, O, and S, and wherein the heterocyclic ring system is unsubstituted or substituted by one or more substituents selected from the group consisting of:

alkoxy,

alkylenedioxy,

hydroxy,

nitro,

oxo,

thioxo,

$-R_4$,

$-Y-R_4$,

$-X-Y-R_4$,

$=N-Q-R_4$,

=N-CN, and

=N-OH;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

-O-C(O)-O-,

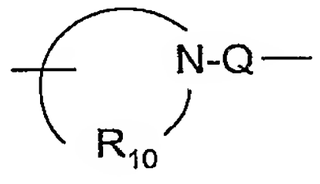
$-O-S(O)_2-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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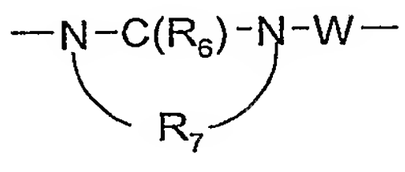

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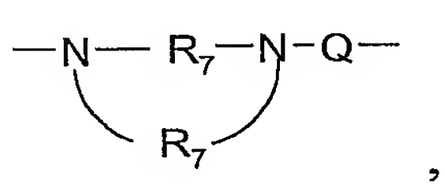

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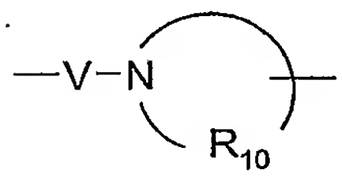
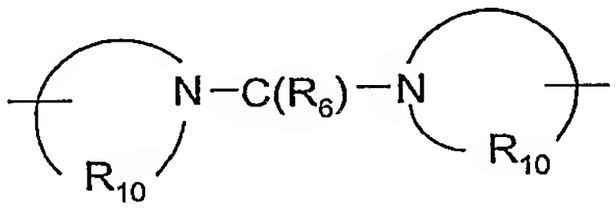


, and

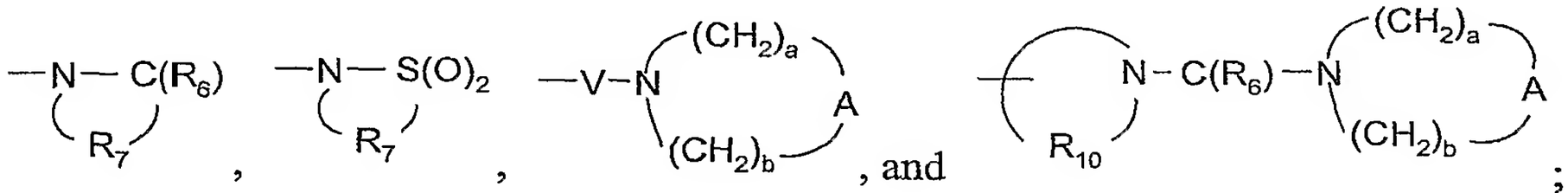


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl,

heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



, and ;

A is selected from the group consisting of -O-, -C(O)-, -$S(O)_{0-2}$-, -CH_2-, and -$N(R_4)$-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, and -$C(R_6)$-$N(OR_9)$-;

V is selected from the group consisting of a bond, -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-;

each a and each b is independently an integer from 1 to 6 with the proviso that a + b in each ring is ≤ 7;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene; and

R is selected from the group consisting of hydrogen, alkyl, alkoxy, trifluoromethyl, chloro, fluoro, and hydroxy;

or a pharmaceutically acceptable salt thereof.

For any of the compounds presented herein, each one of the following variables (e.g., X, Y, Y', R_A, R_B, R', R", R_1, R_2, Q, R_4, R_{3b}, G, and so on) in any of its embodiments can be combined with any one or more of the other variables in any of their embodiments and associated with any one of the formulas described herein, as would be understood by one of skill in the art. Each of the resulting combinations of variables is an embodiment of the present invention.

In some embodiments of Formula I or Formula II, R' is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

-O-C(O)-O-,

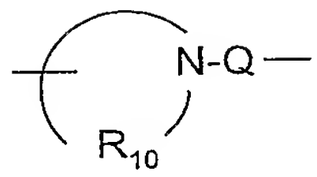
$-O-S(O)_2-$,

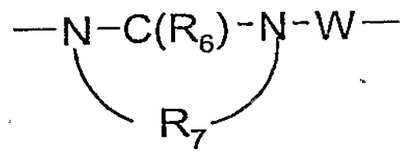
$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,


,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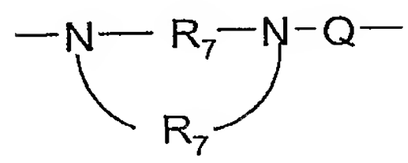
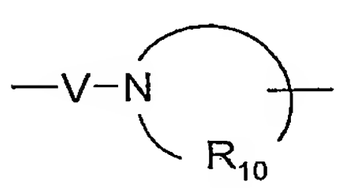
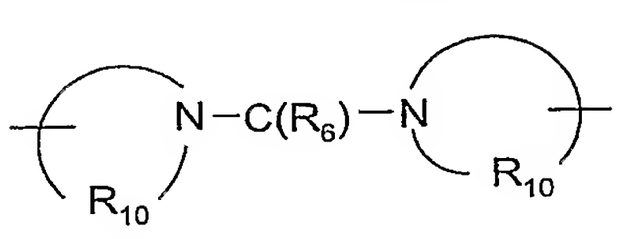
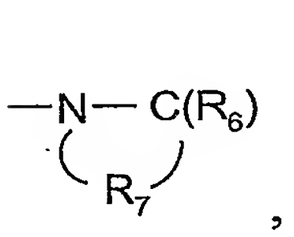

,


, and


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of: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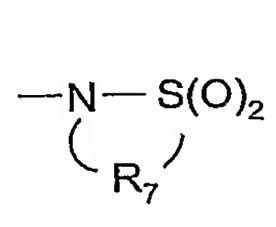
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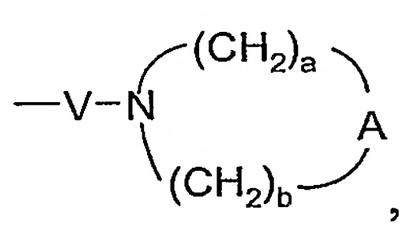
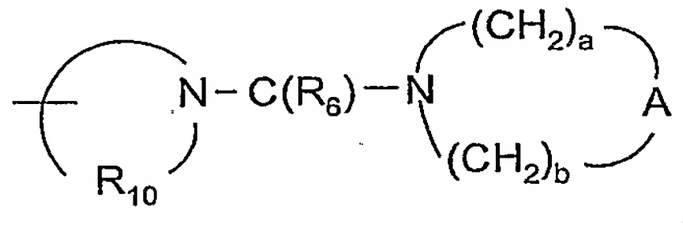

, and


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -$S(O)_{0-2}$-, -CH_2-, and -$N(R_4)$-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, and -$C(R_6)$-$N(OR_9)$-;

V is selected from the group consisting of a bond, -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

In some embodiments of Formula I or Formula II, R" is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

-O-C(O)-O-,

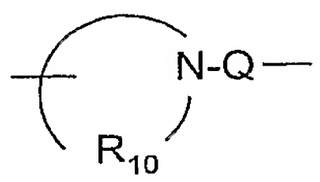
-O-$S(O)_2$-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

$-C(R_6)-N(OR_9)-$,



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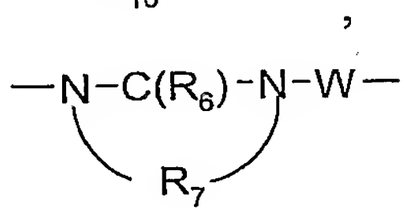

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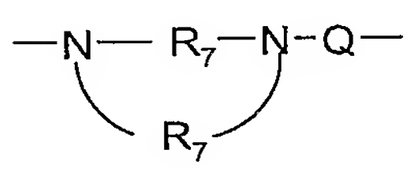

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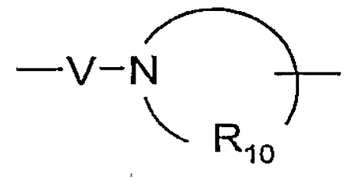
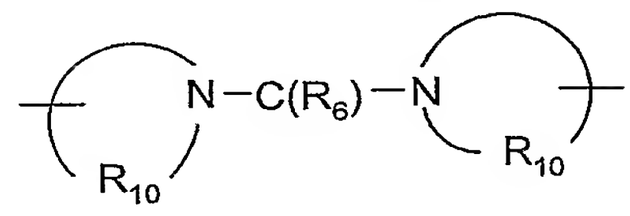


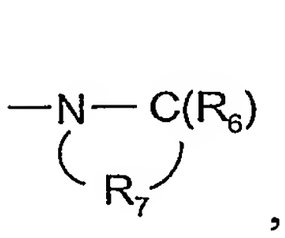
, and



;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



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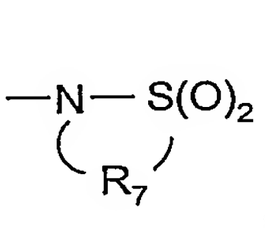

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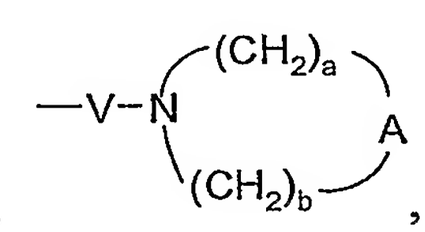
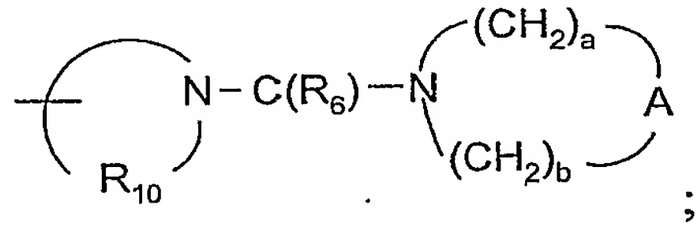


, and



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

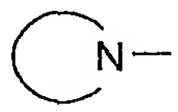
A is selected from the group consisting of -O-, -C(O)-, -$S(O)_{0-2}$-, -CH_2-, and -$N(R_4)$-;

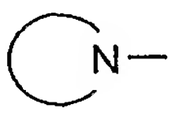
Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, and -$C(R_6)$-$N(OR_9)$-;

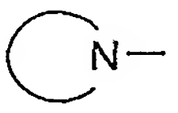
V is selected from the group consisting of a bond, -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

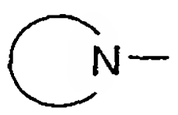
W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-; and

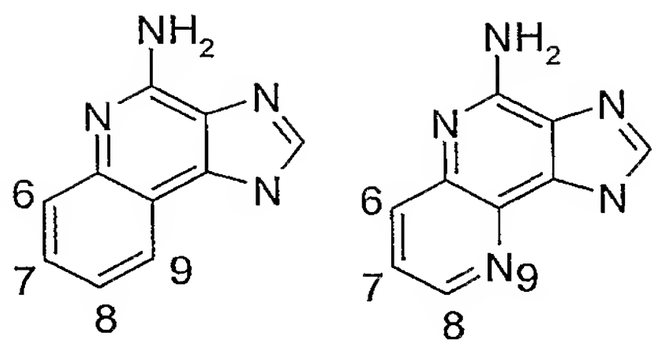
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

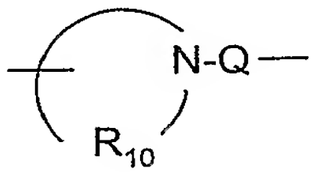
In some embodiments, including any one of the above embodiments of Formulas I, II, IIa, III, or IV, the heterocyclic ring system,  , contains 4 to 13 ring atoms, in some embodiments the heterocyclic ring system contains 4 to 12 ring atoms, and in some embodiments the heterocyclic ring system contains 4 to 11 ring atoms.

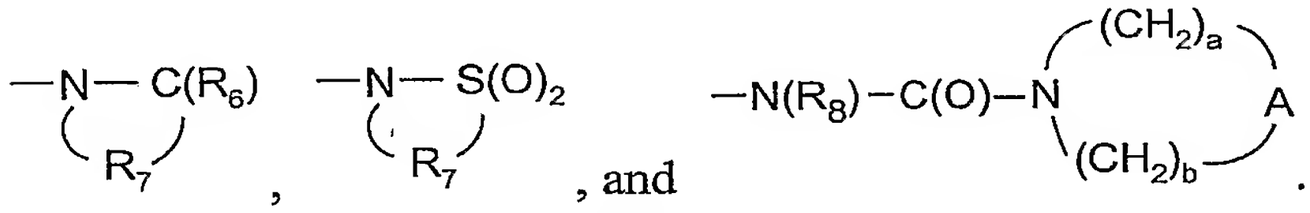
In some embodiments, including any one of the above embodiments of Formulas I, II, IIa, III, or IV, the heterocyclic ring system,  , is a 4 to 9 membered monocyclic ring, in some embodiments the heterocyclic ring system is a 6 to 11 membered bicyclic ring, and in some embodiments the heterocyclic ring system is an 8 to 14 membered tricyclic ring.

In some embodiments, including any one of the above embodiments of Formulas I, II, IIa, III, or IV, the heterocyclic ring system,  , is a 5 to 7 membered monocyclic ring.

In some embodiments, including any one of the above embodiments of Formulas II, IIa, III, or IV,  is at the 7-position; wherein the 7-position is as shown in the following structures:



In some embodiments, including any one of the above embodiments of Formulas IIa, III, or IV, R_1 is selected from the group consisting of alkyl, hydroxyalkyl, alkoxyalkylenyl, arylalkylenyl, aryloxyalkylenyl, heterocyclylalkylenyl, -X-Y-R_4, and -X-R_5; wherein X is alkylene; Y is selected from the group consisting of -S(O)$_{0-2}$-, -N(R_8)-Q-, and  ; R_4 is selected from the group consisting of alkyl, aryl, and heteroaryl; and R_5 is selected from the group consisting of

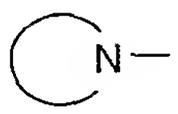


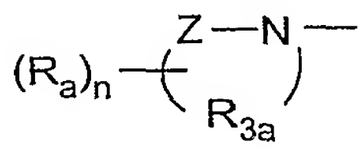
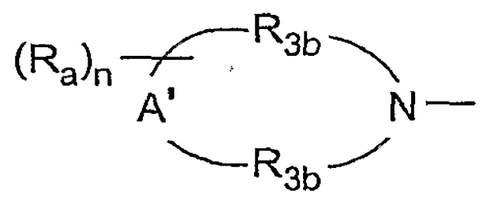
For certain embodiments, including any one of the above embodiments of Formulas IIa, III, or IV, R_1 is selected from the group consisting of alkyl, hydroxyalkyl, alkoxyalkylenyl, and heterocyclylalkylenyl. For certain of these embodiments, R_1 is selected from the group consisting of propyl, 2-methylpropyl, 2-hydroxy-2-methylpropyl, 2,3-dihydroxypropyl, 3-isopropoxypropyl, and tetrahydropyran-4-ylmethyl.

In some embodiments, including any one of the above embodiments of Formulas IIa, III, or IV, R_2 is R_4.

For certain embodiments, including any one of the above embodiments of Formulas IIa, III, or IV, R_2 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl.

For certain embodiments, including any one of the above embodiments of Formulas IIa, III, or IV, R_2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} alkyl-O-C_{1-4} alkylenyl, and HO-C_{1-4} alkylenyl. For certain of these embodiments, R_2 is selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *n*-butyl, ethoxymethyl, methoxymethyl, 2-methoxyethyl, hydroxymethyl, and 2-hydroxyethyl.

In some embodiments, including any one of the above embodiments of Formulas I, II, IIa, III, or IV,  is selected from the group consisting of:

 and  ;

wherein:

Z is selected from the group consisting of -C(O)-, -C(S)-, -S(O)$_{0-2}$-, -OC(O)-, -N(Q-R_4)-C(O)-, -N(Q-R_4)-C(S)-, and -N(Q-R_4)-S(O)$_2$-;

A' is selected from the group consisting of -O-, -C(O)-, -CH_2-, -S(O)$_{0-2}$-, -N(Q-R_4)-, and -C(O)-N(Q-R_4)-;

R_{3a} is C_{2-7} alkylene;

each R_{3b} is independently C_{1-5} alkylene wherein both R_{3b} groups combined have a total of up to seven carbon atoms;

R_a is selected from the group consisting of:

alkoxy,

alkylenedioxy,

hydroxy,

nitro,

oxo,

thioxo,

-R_4,

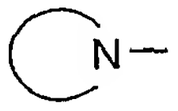
-Y-R_4,

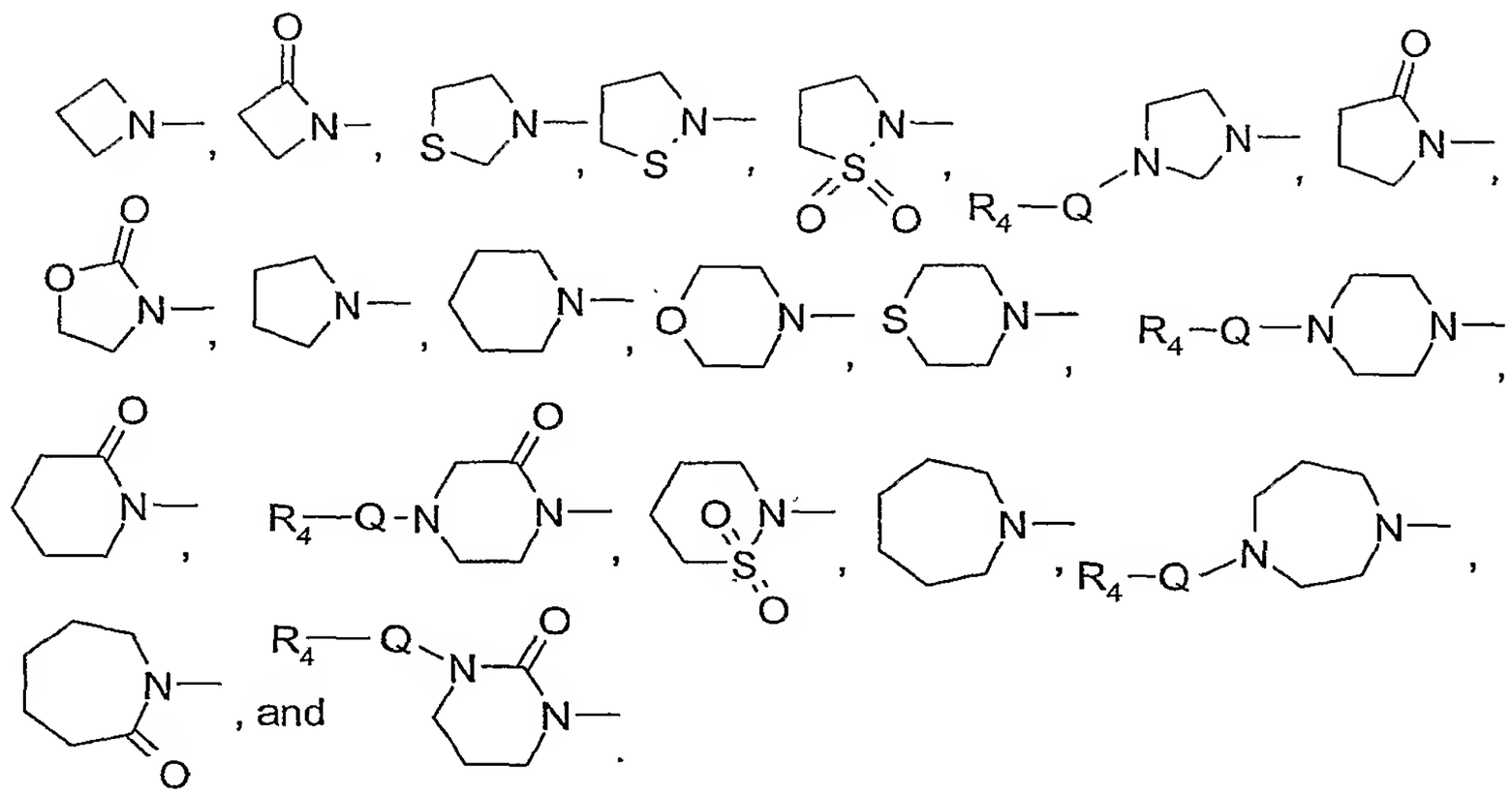
-X-Y-R_4,

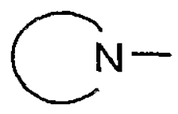
=N-Q-R_4,

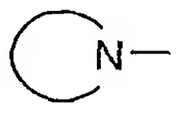
=N-CN, and

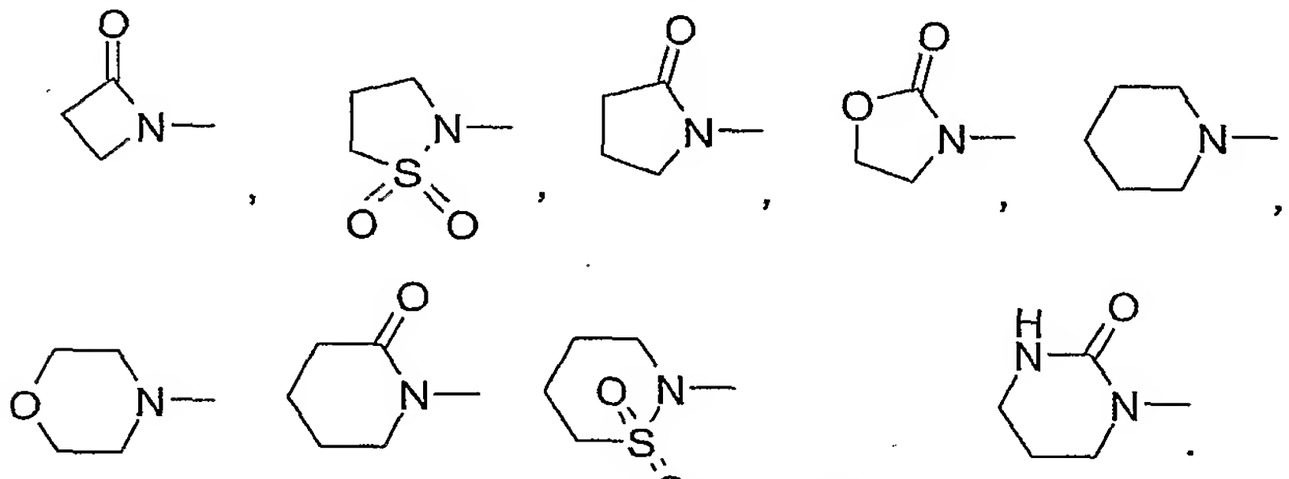
=N-OH; and

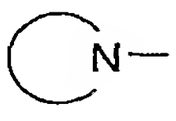
n is 0 or 1; wherein R_4, Q, X, and Y are as defined in Formulas I-IV. In certain of these embodiments R_a is hydroxy, alkoxy, oxo, or R_4. In certain embodiments n is 0. In certain embodiments R_4-Q- is selected from the group consisting of hydrogen, alkyl, acyl, alkylsulfonyl, and arylsulfonyl. In certain embodiments  is selected from the group consisting of:

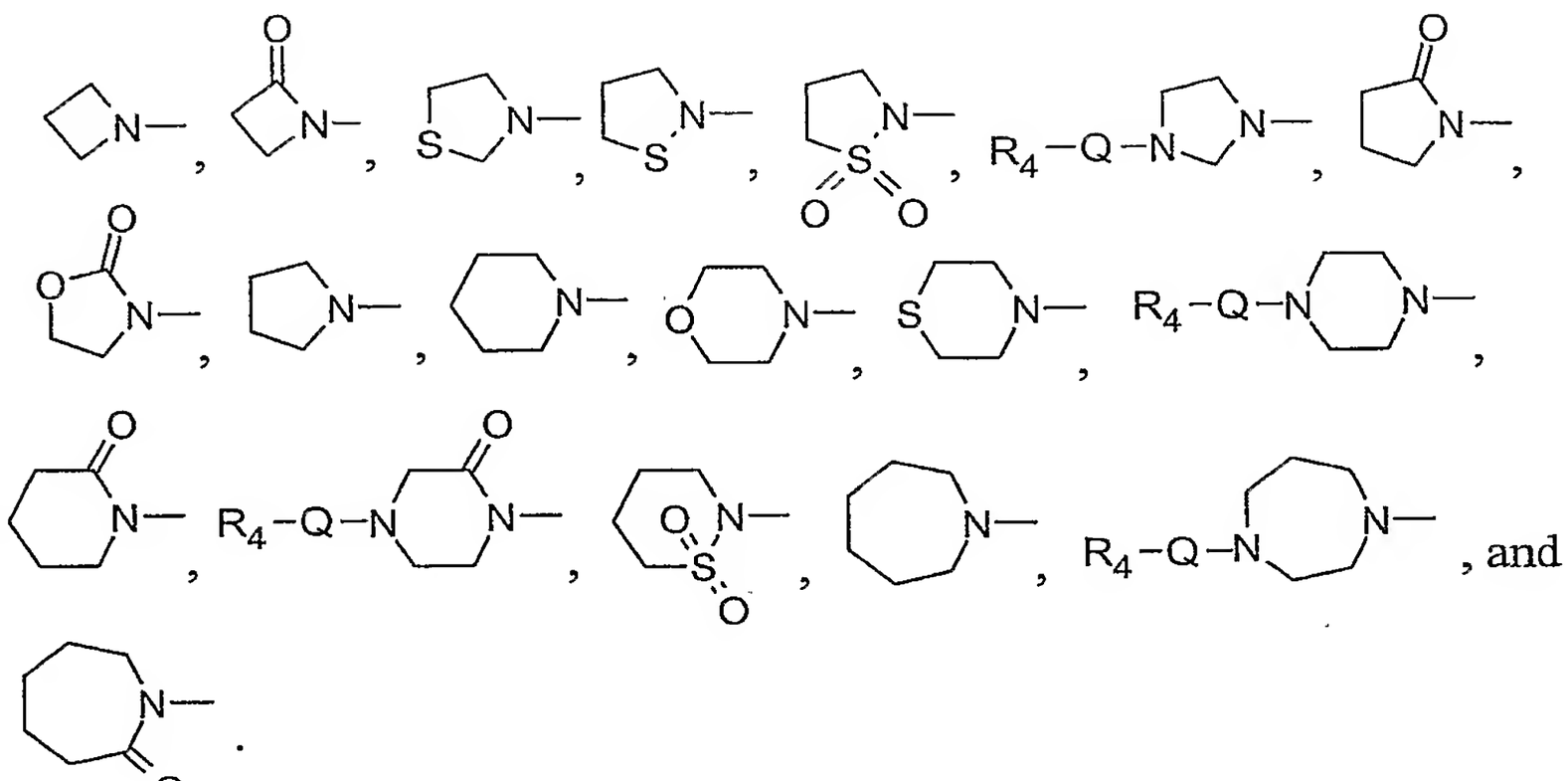


wherein R_4, and Q are as defined in Formulas I-IV, and in certain of these embodiments R_4-Q- is selected from the group consisting of hydrogen, alkyl, acyl, alkylsulfonyl, and arylsulfonyl. In certain of these embodiments,  is at the 7-position.

In certain embodiments, including any one of the above embodiments,  is selected from the group consisting of:



In certain embodiments, including any one of the above embodiments except where excluded,  is selected from the group consisting of:

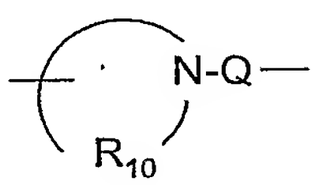


, and

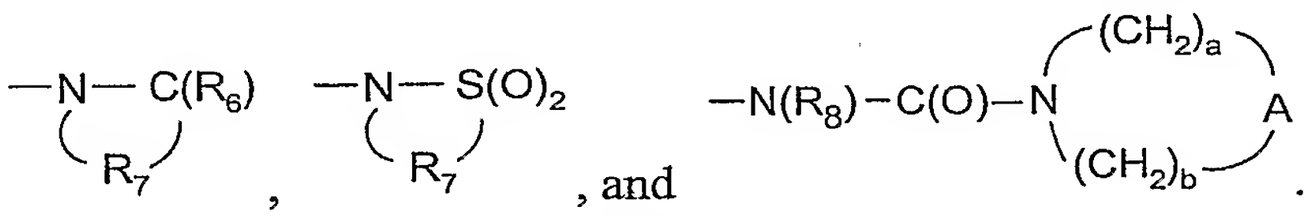
.

In some embodiments, including any one of the above embodiments of Formulas I, II, IIa, III, or IV, R is hydrogen.

In some embodiments, including any one of the above embodiments of Formulas IIa, III, or IV, R_1 is selected from the group consisting of alkyl, hydroxyalkyl, alkoxyalkylenyl, arylalkylenyl, aryloxyalkylenyl, heterocyclylalkylenyl, -X-Y-R_4, and -X-R_5; wherein X is alkylene; Y is selected from the group consisting of

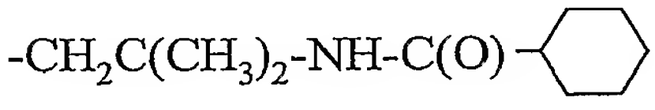


-$S(O)_{0-2}$-, -$N(R_8)$-Q-, and ; R_4 is selected from the group consisting of alkyl, aryl, and heteroaryl; and R_5 is selected from the group consisting of

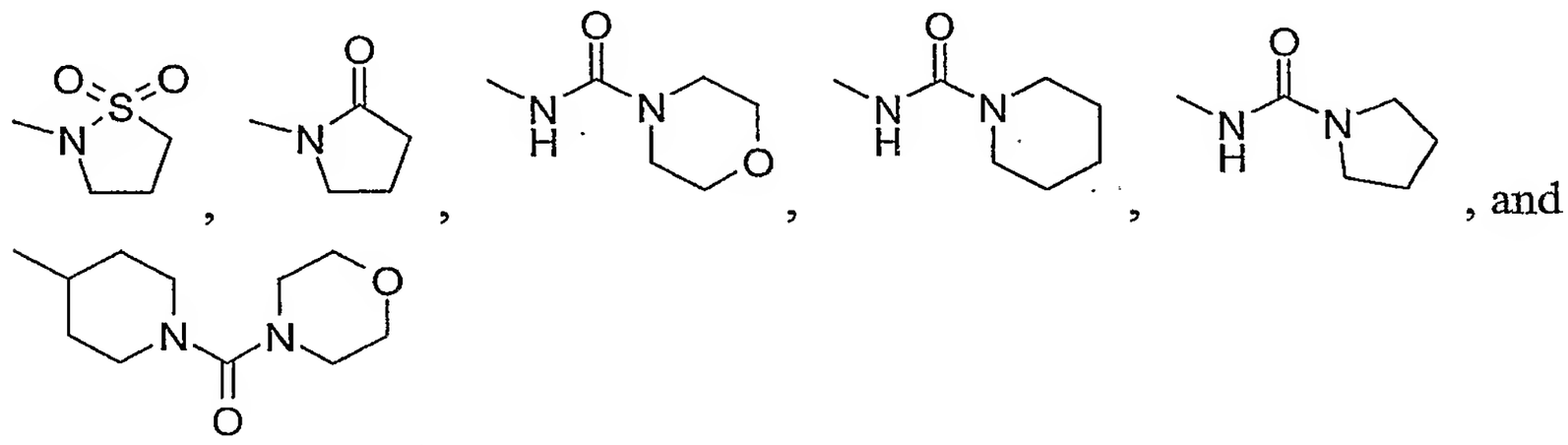


In certain embodiments R_1 is -X-Y-R_4. In certain embodiments -X- is C_{2-6} alkylene. In certain embodiments R_1 is -X-Y-R_4, and -X- is C_{2-6} alkylene. In certain embodiments -X- is C_{2-4} alkylene. In certain embodiments -X- is -$CH_2C(CH_3)_2$-. In certain embodiments -Y- is –$S(O)_{0-2}$- or -NR_8-Q-. In certain embodiments Y- is -$N(R_8)$-C(O)-, -$N(R_8)$-$S(O)_2$-, or -$N(R_8)$-C(O)-$N(R_8)$-. In certain embodiments R_8 is hydrogen. In certain embodiments R_4 is C_{1-6} alkyl. In certain embodiments R_4 is methyl, isopropyl, or cyclohexyl. In certain embodiments -X- is C_{2-6} alkylene, -Y- is -NH-$S(O)_2$-, and R_4 is C_{1-6} alkyl. In certain embodiments -X- is -$CH_2C(CH_3)_2$-, Y- is -NH-$S(O)_2$-, and R_4 is C_{1-6} alkyl. In certain embodiments -X- is C_{2-6} alkylene, -Y- is -NH-C(O)-, and R_4 is C_{1-6} alkyl. In certain

embodiments -X- is $-CH_2C(CH_3)_2-$, -Y- is -NH-C(O)-, and R_4 is C_{1-6} alkyl. In certain embodiments -X- is C_{2-6} alkylene, -Y- is -NH-C(O)-NH-, and R_4 is C_{1-6} alkyl. In certain embodiments -X- is $-CH_2C(CH_3)_2-$, -Y- is -NH-C(O)-NH-, and R_4 is C_{1-6} alkyl. In certain embodiments R_1 is $-(CH_2)_4$-NH-$S(O)_2$-CH_3, $-CH_2C(CH_3)_2$-NH-$S(O)_2$-CH_3, $-CH_2C(CH_3)_2$-NH-C(O)-NH-$CH(CH_3)_2$, or



In certain embodiments, including any one of the above embodiments of Formulas IIa, III, or IV, R_1 is -X-R_5. In certain embodiments, -X- is C_{2-6} alkylene. In certain embodiments, -X- is C_{2-4} alkylene. In certain embodiments, -X- is $-CH_2C(CH_3)_2-$. In certain embodiments, R_5 is . In certain embodiments, R_5 is selected from the group consisting of:



In some embodiments, including any one of the above embodiments of Formulas IIa, III, or IV, R_1 is alkyl, hydroxyalkyl, alkoxyalkylenyl, or aryloxyalkylenyl. In certain embodiments R_1 is C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-4} alkyl-O-C_{1-4} alkylenyl, or aryl-O-C_{1-4} alkylenyl. In certain embodiments R_1 is alkyl or hydroxyalkyl. In certain embodiments R_1 is C_{1-4} alkyl or C_{1-4} hydroxyalkyl. In certain embodiments R_1 is 2-methylpropyl, 2-hydroxy-2-methylpropyl, 3-methoxypropyl, or phenoxyethyl. In certain embodiments R_1 is 2-methylpropyl. In certain embodiments R_1 is 2-hydroxy-2-methylpropyl.

In some embodiments, including any one of the above embodiments of Formulas IIa, III, or IV, R_2 is R_4. In certain embodiments R_2 is hydrogen, alkyl or alkoxyalkylenyl. In certain embodiments R_2 is hydrogen, C_{1-4} alkyl, or C_{1-4} alkyl-O-C_{1-4} alkylenyl. In certain embodiments R_2 is methyl, ethyl, n-propyl, n-butyl, 2-methoxyethyl, methoxymethyl, or ethoxymethyl.

For certain embodiments, R is selected from the group consisting of hydrogen, alkyl, alkoxy, trifluoromethyl, chloro, fluoro, and hydroxy.

For certain embodiments, R is hydrogen.

For certain embodiments, R_a is selected from the group consisting of alkoxy, alkylenedioxy, hydroxy, nitro, oxo, thioxo, $-R_4$, $-Y-R_4$, $-X-Y-R_4$, $=N-Q-R_4$, =N-CN, and =N-OH.

For certain embodiments, R_a is hydroxy, alkoxy, oxo, or R_4.

For certain embodiments, R_{3a} is C_{2-7} alkylene.

For certain embodiments, R_{3a} is C_{2-5} alkylene.

For certain embodiments, R_{3b} is C_{1-5} alkylene wherein both R_{3b} groups combined have a total of up to seven carbon atoms. For certain embodiments, both R_{3b} groups combined have a total of up to five carbon atoms.

For certain embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo.

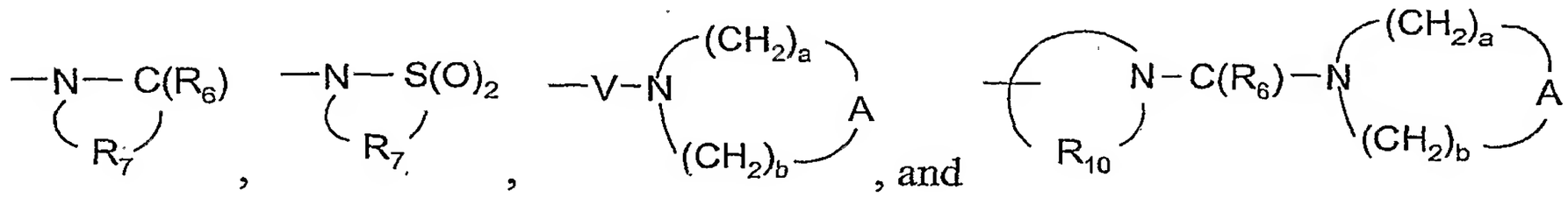
For certain embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy,

arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo.

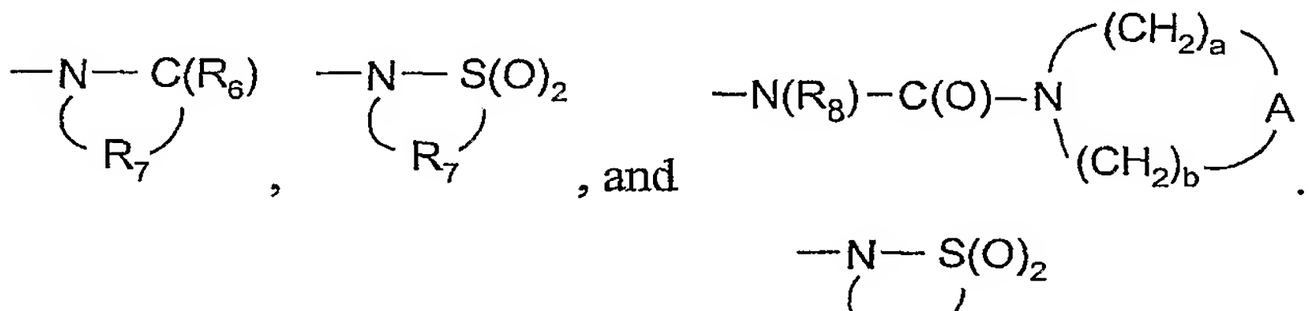
For certain embodiments, R_4 is selected from the group consisting of alkyl, aryl, and heteroaryl.

For certain embodiments, R_4 is alkyl or aryl.

For certain embodiments, R_5 is selected from the group consisting of:

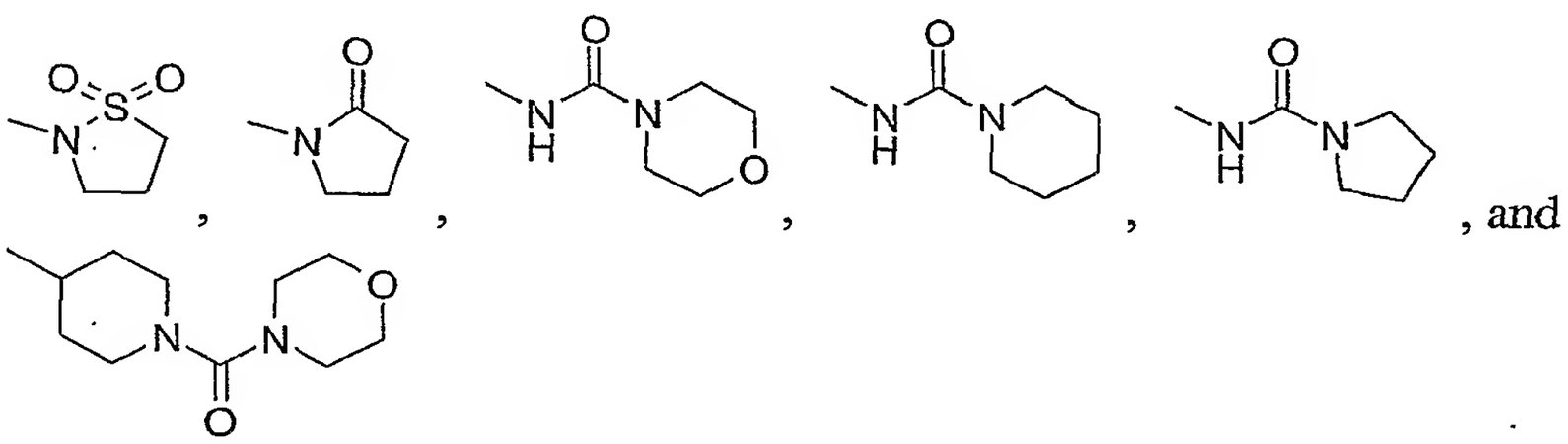

, and .

For certain embodiments, R_5 is selected from the group consisting of:


, and .

In certain embodiments, R_5 is .

In certain embodiments, R_5 is selected from the group consisting of:


, and

.

For certain embodiments, R_6 is selected from the group consisting of =O and =S.

For certain embodiments, R_6 is =O.

For certain embodiments, R_7 is C_{2-7} alkylene.

For certain embodiments, R_7 is C_{2-3} alkylene.

For certain embodiments, R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl.

For certain embodiments, particularly in $-N(R_8)-Q-$ and $-C(R_6)-N(R_8)-$, R_8 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and alkoxyalkylenyl.

For certain embodiments, R_8 is hydrogen or C_{1-4} alkyl.

For certain embodiments, R_9 is selected from the group consisting of hydrogen and alkyl.

For certain embodiments, R_9 is hydrogen or methyl.

For certain embodiments, R_{10} is C_{3-8} alkylene.

For certain embodiments, R_{10} is C_5 alkylene.

For certain embodiments, A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}$-, $-CH_2$-, and $-N(R_4)$-.

For certain embodiments, A is -O-, $-CH_2$-, or -C(O)-.

For certain embodiments, A' is selected from the group consisting of -O-, -C(O)-, $-CH_2$-, $-S(O)_{0-2}$-, $-N(Q-R_4)$-, and $-C(O)-N(Q-R_4)$-.

For certain embodiments, A' is -O-.

For certain embodiments, Q is selected from the group consisting of a bond, $-C(R_6)$-, $-C(R_6)-C(R_6)$, $-S(O)_2$-, $-C(R_6)-N(R_8)-W$-, $-S(O)_2-N(R_8)$-, $-C(R_6)$-O-, and $-C(R_6)-N(OR_9)$-.

For certain embodiments, Q is -C(O)-, $-S(O)_2$-, or $-C(O)-N(R_8)$-.

For certain embodiments, V is selected from the group consisting of $-C(R_6)$-, $-O-C(R_6)$-, $-N(R_8)-C(R_6)$-, and $-S(O)_2$-.

For certain embodiments, V is -C(O)-.

For certain embodiments, V is $-N(R_8)-C(O)$-.

For certain embodiments, W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-.

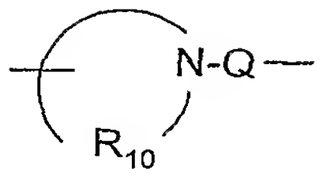
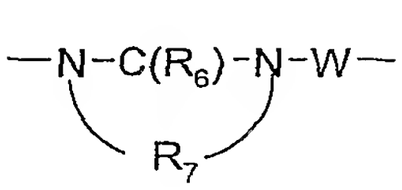
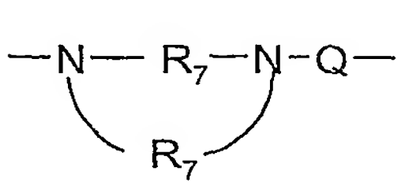
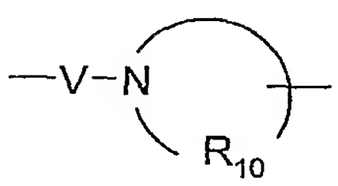
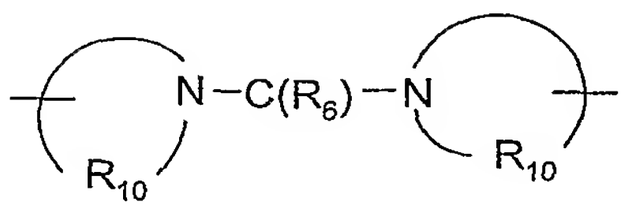
For certain embodiments, W is a bond.

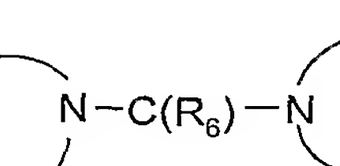
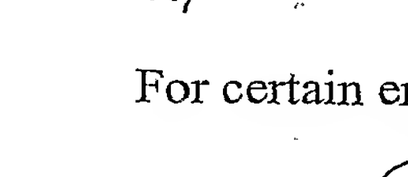
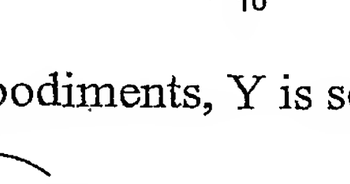
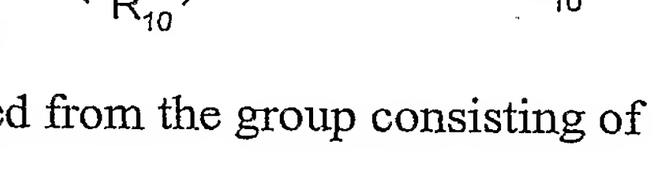
For certain embodiments, X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups.

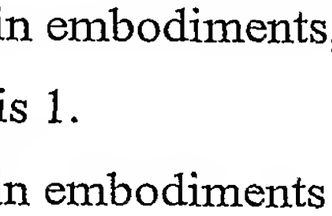
For certain embodiments, X is alkylene.

For certain embodiments, X is C_{2-6} alkylene.

For certain embodiments, Y is selected from the group consisting of -O-, $-S(O)_{0-2}$-, $-S(O)_2-N(R_8)$-, $-C(R_6)$-, $-C(R_6)$-O-, $-O-C(R_6)$-, -O-C(O)-O-, $-O-S(O)_2$-, $-N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-, -O-$C(R_6)$-$N(R_8)$-, -$C(R_6)$-$N(OR_9)$-,  ,  ,  ,  , and  .

For certain embodiments, Y is selected from the group consisting of -$S(O)_{0-2}$-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-, -$C(R_6)$-O-, -O-$C(R_6)$-, -O-C(O)-O-, -O-$S(O)_2$-, -$N(R_8)$-Q-, -$C(R_6)$-$N(R_8)$-, -O-$C(R_6)$-$N(R_8)$-, -$C(R_6)$-$N(OR_9)$-,  ,  ,  ,  , and  .

For certain embodiments, Y is selected from the group consisting of -$S(O)_{0-2}$-, -$N(R_8)$-Q-, and  .

For certain embodiments, Y is –$S(O)_{0-2}$- or -NR_8-Q-.

For certain embodiments, Y is -$N(R_8)$-C(O)-, -$N(R_8)$-$S(O)_2$-, or -$N(R_8)$-C(O)-$N(R_8)$-.

For certain embodiments, Z is selected from the group consisting of -C(O)-, -C(S)-, -$S(O)_{0-2}$-, -OC(O)-, -$N(Q\text{-}R_4)$-C(O)-, -$N(Q\text{-}R_4)$-C(S)-, and -$N(Q\text{-}R_4)$-$S(O)_2$-.

For certain embodiments, Z is -C(O)-, -$S(O)_{0-2}$-, -OC(O)-, or -$N(Q\text{-}R_4)$-C(O)-.

For certain embodiments, a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

For certain embodiments, a is 2.

For certain embodiments, b is 2.

For certain embodiments, n is 0 or 1. For certain embodiments, n is 0. For certain embodiments, n is 1.

For certain embodiments of the compounds of Formulas I, II, IIa, and III, the –NH_2 group can be replaced by an -NH-G group, as shown in the compound of Formula IV, to form prodrugs. In such embodiments, G is selected from the group consisting of

-C(O)-R'", α-aminoacyl, α-aminoacyl-α-aminoacyl, -C(O)-O-R'", -C(O)-N(R'"")R'", -C(=NY')-R'", -CH(OH)-C(O)-OY', -CH(OC_{1-4} alkyl)Y_0, -CH_2Y_1, and -CH(CH_3)Y_1. In some embodiments G is selected from the group consisting of -C(O)-R'", α-aminoacyl, α-aminoacyl-α-aminoacyl, and -C(O)-O-R'". Preferably, R'" and R'"" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, and benzyl, each of which may be unsubstituted or substituted by one or more substitutents selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, arylC_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl, haloC_{1-4} alkylenyl, haloC_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2. R'"" may also be hydrogen. Preferably, α-aminoacyl is an acyl group derived from an amino acid selected from the group consisting of racemic, D-, and L-amino acids. Preferably, Y' is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl. Preferably, Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxyC_{1-6} alkylenyl, aminoC_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylaminoC_{1-4} alkylenyl, and di-*N,N*-C_{1-6} alkylaminoC_{1-4} alkylenyl. Preferably, Y_1 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl.

For certain embodiments, including any one of the above embodiments containing -NH-G, G is -C(O)-R'", α-aminoacyl, α-aminoacyl-α-aminoacyl, or -C(O)-O-R'".

Herein, "non-interfering" means that the ability of the compound or salt, which includes a non-interfering substituent, to modulate the biosynthesis of one or more cytokines is not destroyed by the non-interfering substitutent. Illustrative non-interfering R' groups include those described above for R_1 in Formulas IIa-IV. Illustrative non-interfering R" groups include those described above for R_2 in Formulas IIa-IV.

As used herein, the terms "alkyl", "alkenyl", "alkynyl", and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, e.g., cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl,

cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene", "alkenylene", and "alkynylene" are the divalent forms of the "alkyl", "alkenyl", and "alkynyl" groups defined above. The terms, "alkylenyl", "alkenylenyl", and "alkynylenyl" are use when "alkylene", "alkenylene", and "alkynylene", respectively, are substituted. For example, an arylalkylenyl group comprises an alkylene moiety to which an aryl group is attached. In another example, hydroxyalkylenyl, haloalkylenyl, and haloalkyleneoxy have the same meaning as hydroxyalkyl, haloalkyl, and haloalkoxy, respectively.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-". Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

Unless otherwise indicated, the term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). In some embodiments, the term "heteroaryl" includes a ring or ring system that contains 2 to 12 carbon atoms, 1 to 3 rings, 1 to 4 heteroatoms, and O, S, and/or N as the heteroatoms. Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

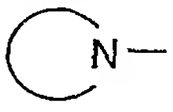
The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. In some embodiments, the term "heterocyclyl" includes a ring or ring system that contains 2 to 12 carbon atoms, 1 to 3 rings, 1 to 4 heteroatoms, and O, S, and N as the heteroatoms. Exemplary heterocyclyl groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl,

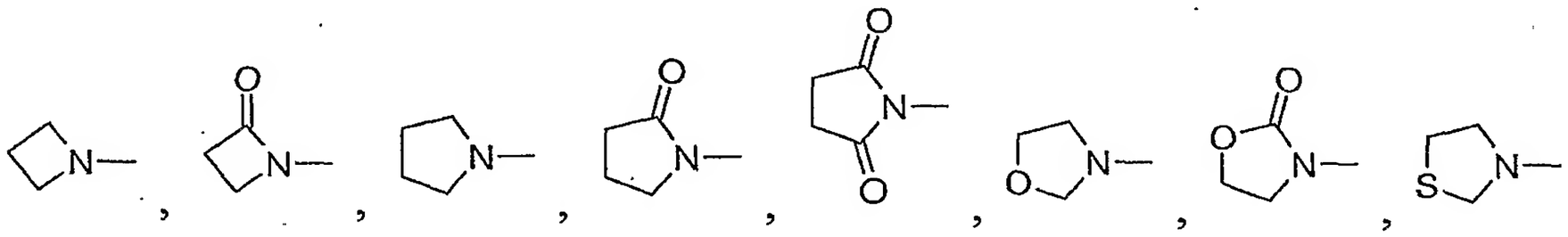
isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl (azepanyl), 1,4-oxazepanyl, homopiperazinyl (diazepanyl), 1,3-dioxolanyl, aziridinyl, azetidinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, 3-azabicyclo[3.2.2]non-3-yl, and the like.

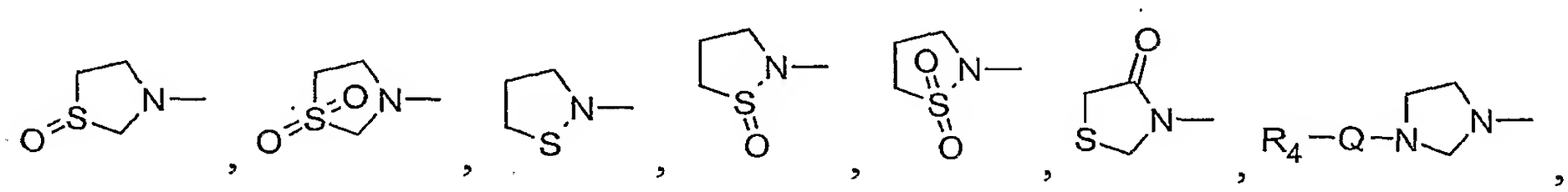
The term "heterocyclyl" includes bicylic and tricyclic heterocyclic ring systems. Such ring systems include fused and/or bridged rings and spiro rings. Fused rings can include, in addition to a saturated or partially saturated ring, an aromatic ring, for example, a benzene ring. Spiro rings include two rings joined by one spiro atom and three rings joined by two spiro atoms.

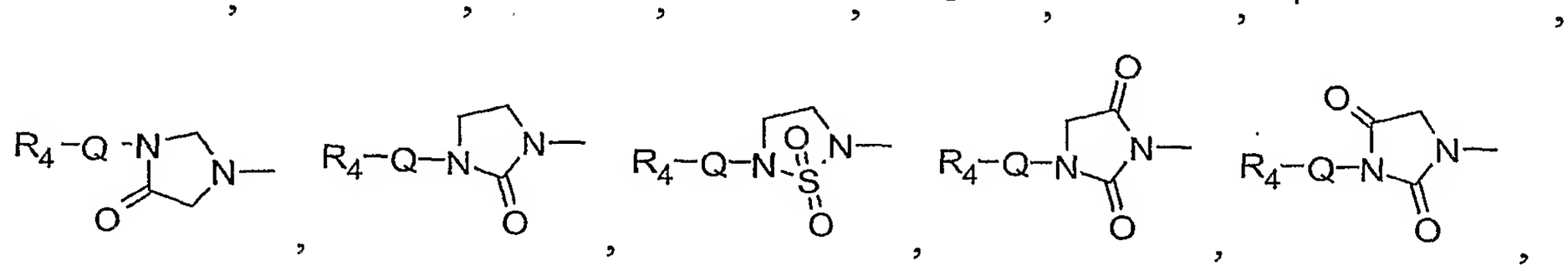
When "heterocyclyl" contains a nitrogen atom, the point of attachment of the heterocyclyl group may be the nitrogen atom.

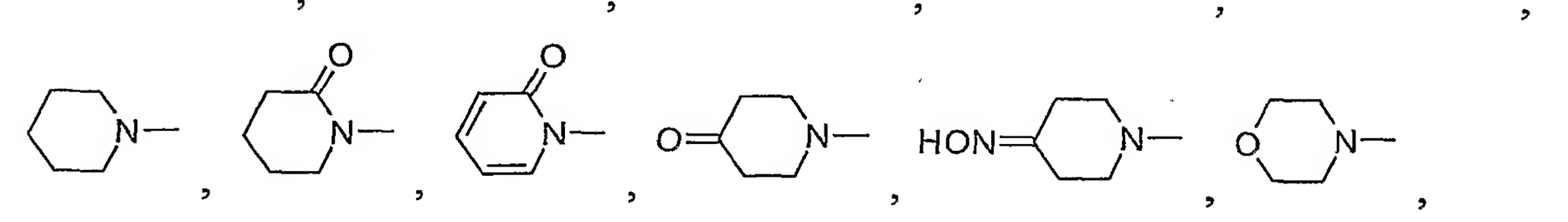
Bicylic and tricyclic rings of the heterocyclic ring system,  , include fused and/or bridged rings and spiro rings. Fused rings can include, in addition to a saturated or partially saturated ring, an aromatic ring, for example, a benzene ring. Spiro rings include two rings joined by one spiro atom and three rings joined by two spiro atoms.

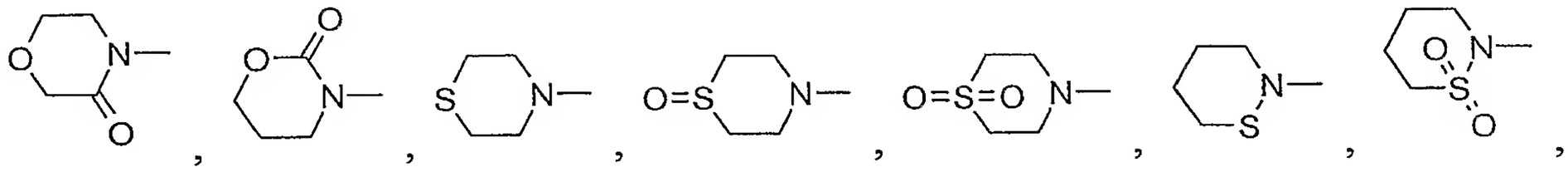
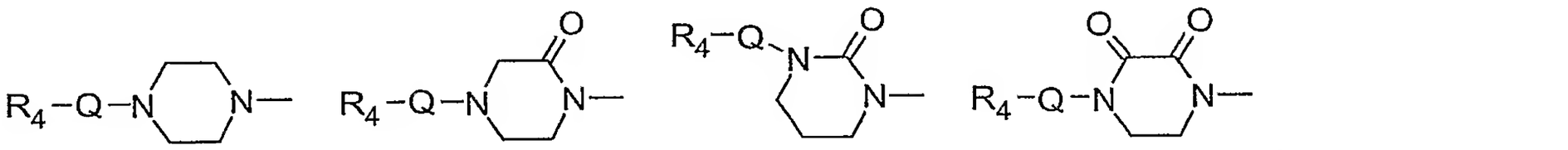
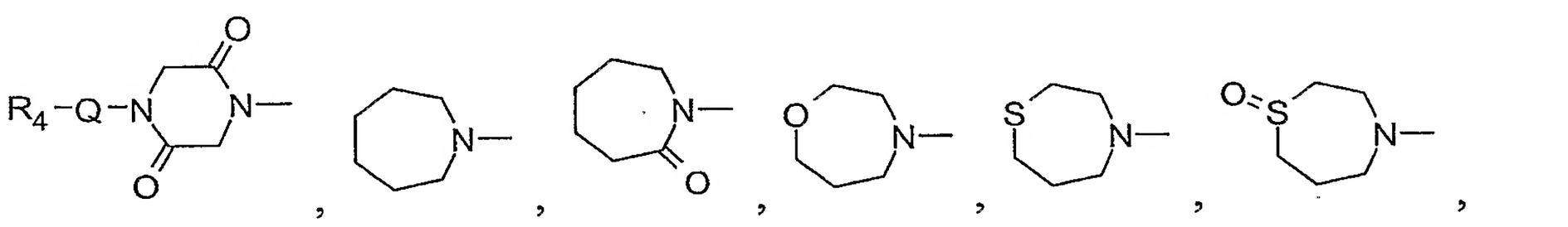
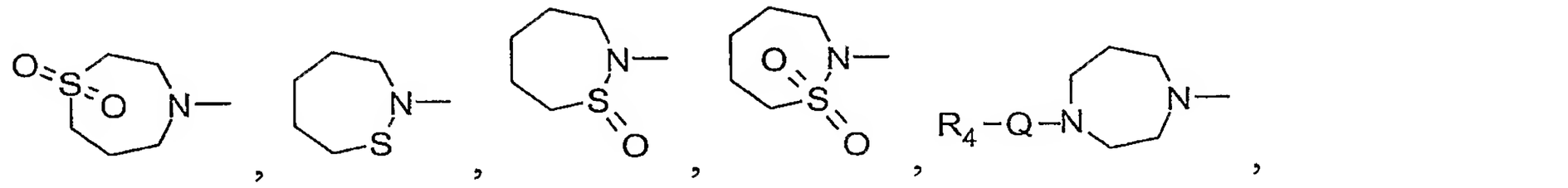
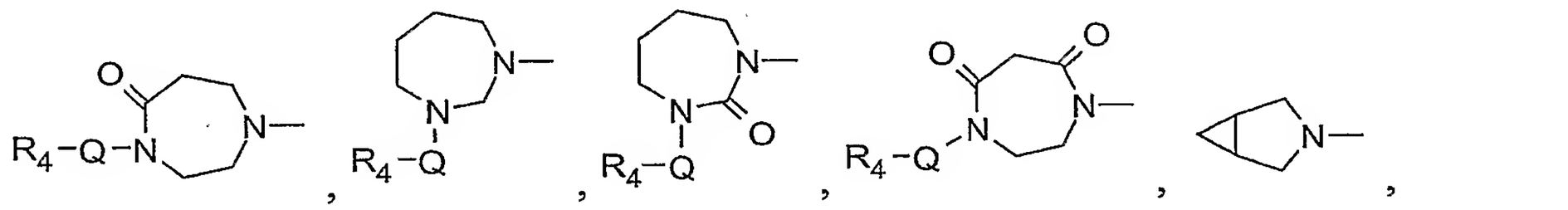
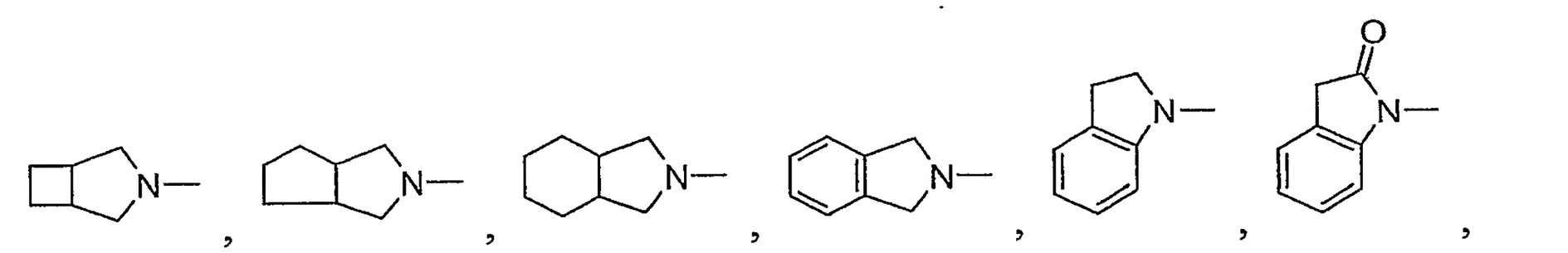
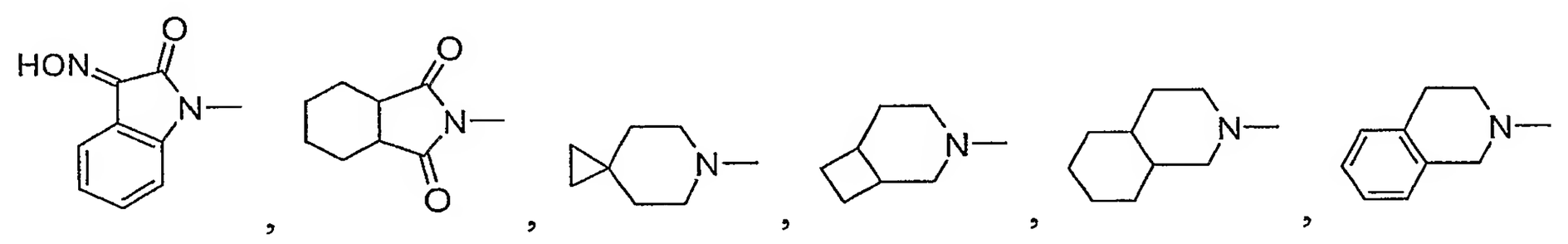
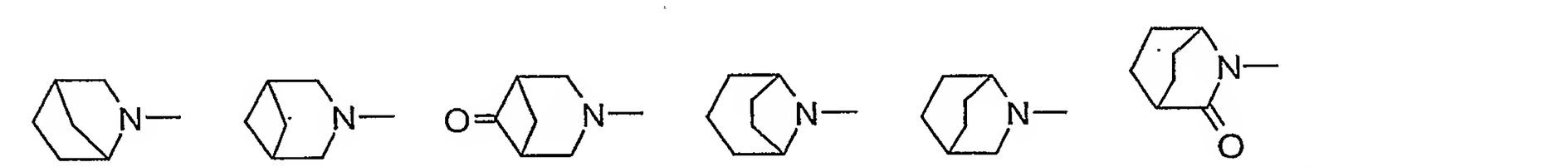
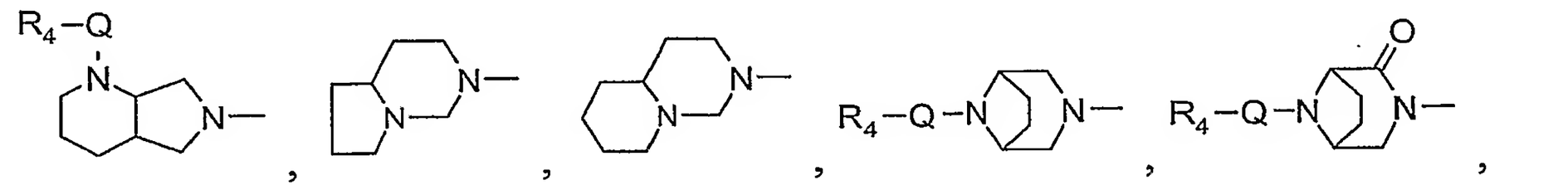
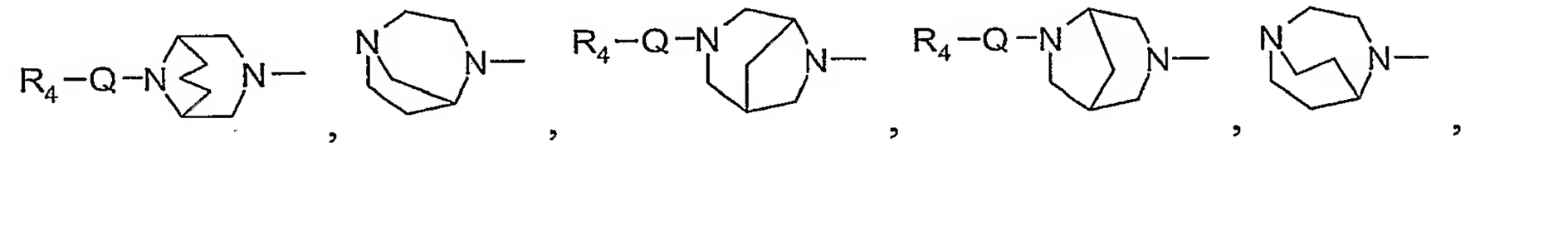
Illustrative heterocyclic ring systems,  , include, for example, the following:

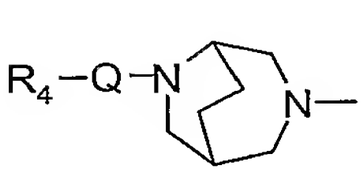
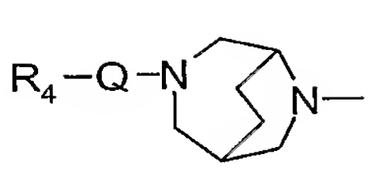
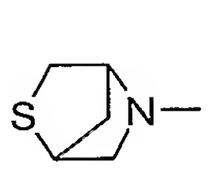
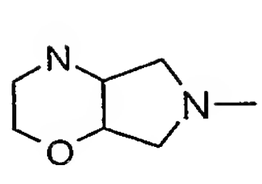
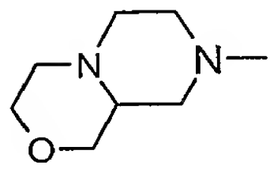
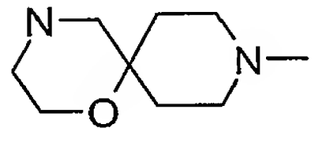
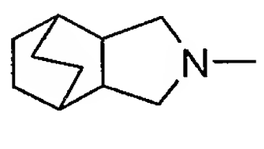






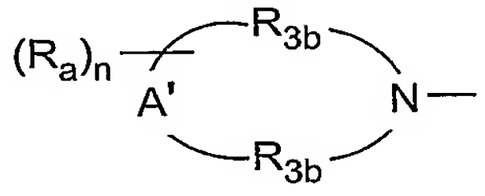


wherein R_4, and Q are as defined above. In some examples Q is a bond, and in some examples Q is a bond and R_4 is hydrogen or alkyl.

The terms "arylene", "heteroarylene", and "heterocyclylene" are the divalent forms of the "aryl", "heteroaryl", and "heterocyclyl" groups defined above. The terms, "arylenyl", "heteroarylenyl", and "heterocyclylenyl" are used when "arylene", "heteroarylene," and "heterocyclylene", respectively, are substituted. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

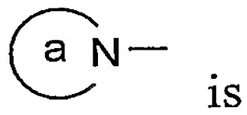
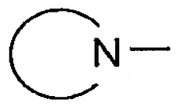
When a group (or substituent or variable) is present more than once in any Formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, for the formula  each R_{3b} group is independently selected. In another example, when an R_1 and an R_2 group both contain an R_4 group, each R_4 group is independently selected. In a further example, when more than one Y group is present and each Y group contains one or more R_7 groups, then each Y group is independently selected, and each R_7 group is independently selected.

The invention is inclusive of the compounds described herein (including intermediates) in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, prodrugs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers. It should be understood that the term "compound" includes any or all of such forms, whether explicitly stated or not (although at times, "salts" are explicitly stated).

The term "prodrug" means a compound that can be transformed in vivo to yield an immune response modifying compound in any of the salt, solvated, polymorphic, or isomeric forms described above. The prodrug, itself, may be an immune response modifying compound in any of the salt, solvated, polymorphic, or isomeric forms

described above. The transformation may occur by vaious mechanisms, such as through a chemical (e.g., solvolysis or hydrolysis, for example, in the blood) or enzymatic biotransformation. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A. C. S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

Preparation of the Compounds

Compounds of the invention can be prepared according to Reaction Scheme I wherein R, R_1, and R_2 are as defined above, and  is  defined above containing a carbonyl, thiocarbonyl, or sulfonyl group adjacent the nitrogen atom. In step (1) of Reaction Scheme I, a 4-chloro-3-nitroquinoline of Formula X is reacted with an amine of Formula R_1-NH_2 to provide a compound of Formula XI. The reaction can be carried out by adding the amine to a solution of a compound of Formula X in a suitable solvent such as anhydrous dichloromethane in the presence of a base such as triethylamine. The reaction can be run at ambient temperature. Compounds of Formula X can be prepared using the synthetic methods described at the beginning of the Example section below.

In step (2) of Reaction Scheme I a compound of Formula XI is reduced to provide a compound of Formula XII. The reduction can be carried out using a conventional heterogeneous hydrogenation catalyst such as platinum on carbon. The reaction can be conveniently carried out on a Parr apparatus in a suitable solvent such as acetonitrile, toluene and/or isopropanol.

Other reduction processes may be used for the reduction in step (2). For example, an aqueous solution of sodium dithionite can be added to a solution or suspension of the compound of Formula XI in a suitable solvent such as ethanol or isopropanol. The reaction can be carried out at an elevated temperature, for example at reflux, or at ambient temperature.

In step (3) of Reaction Scheme I a compound of Formula XII is (i) reacted with an acyl halide of Formula $R_2C(O)Cl$ or $R_2C(O)Br$ and then (ii) cyclized to provide a 1*H*-imidazo compound of Formula XIII. In part (i) the acyl halide is added to a solution of a compound of Formula XII in a suitable solvent such as acetonitrile or anhydrous

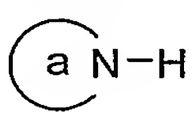
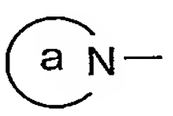
dichloromethane in the presence of a base such as triethylamine. The reaction can be run at a reduced temperature, for example, 0° C, or at ambient temperature. In part (ii) the product of part (i) is heated in an alcoholic solvent in the presence of a base. For example, the product of part (i) is refluxed in ethanol in the presence of excess triethylamine or is heated with methanolic ammonia.

Alternatively, step (3) can be carried out by reacting a compound of Formula XII with a carboxylic acid or an equivalent thereof. Suitable equivalents to carboxylic acid include orthoesters and 1,1-dialkoxyalkyl alkanoates. The carboxylic acid or equivalent is selected such that it will provide the desired R_2 substituent in a compound of Formula XIII. For example, triethyl orthoformate will provide a compound where R_2 is hydrogen, and triethyl orthovalerate will provide a compound where R_2 is butyl. The reaction can be run in the absence of solvent or in an inert solvent such as anhydrous toluene. The reaction is run with sufficient heating to drive off any alcohol or water formed as a byproduct of the reaction. Optionally a catalyst such as pyridine hydrochloride can be utilized.

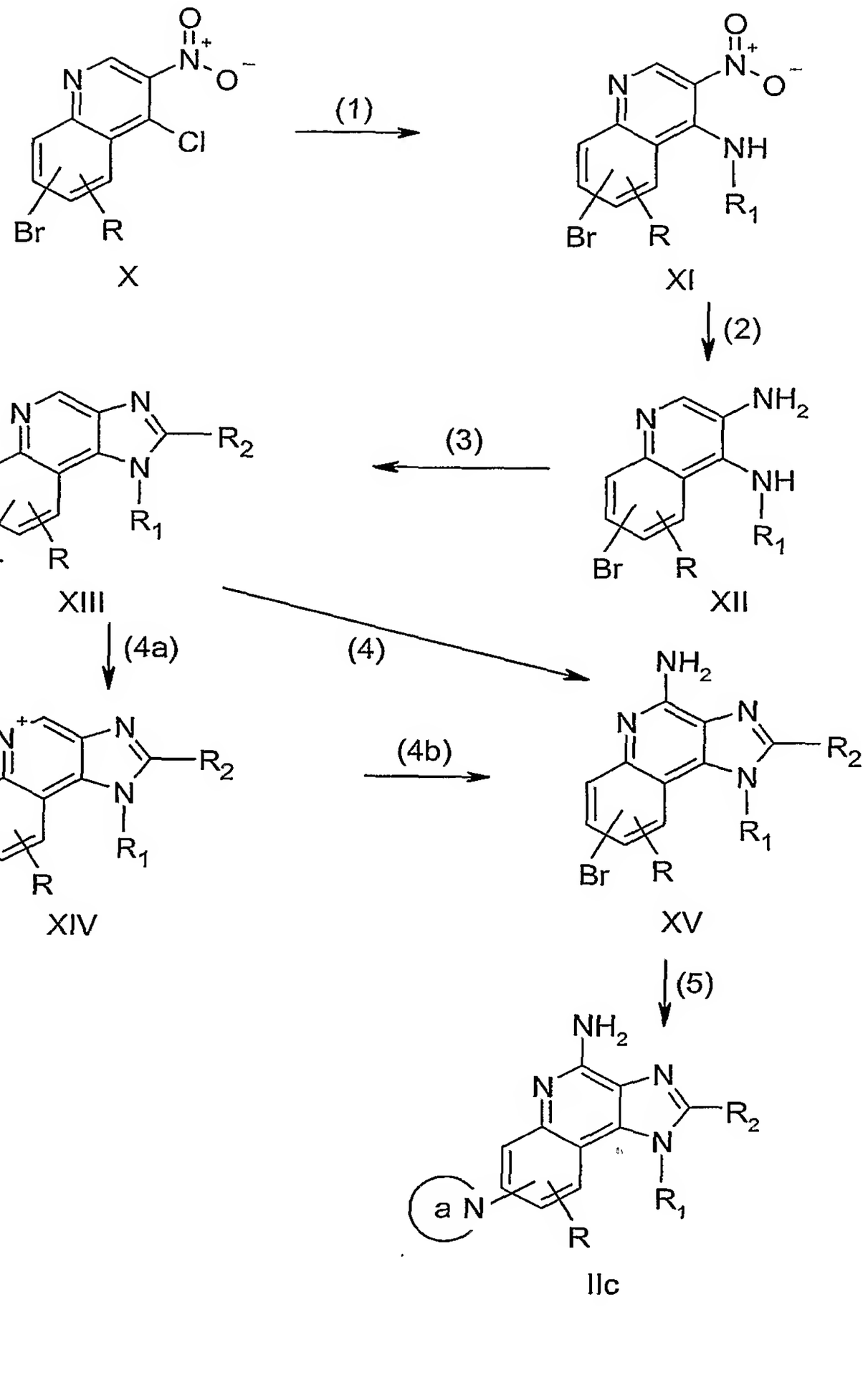
In step (4a) of Reaction Scheme I, a 1*H*-imidazo compound of Formula XIII is oxidized to provide an *N*-oxide of Formula XIV using a conventional oxidizing agent that is capable of forming *N*-oxides. The reaction is carried out by treating a solution of a compound of Formula XIII in a suitable solvent such as chloroform or dichloromethane with 3-chloroperoxybenzoic acid at ambient temperature.

In step (4b) of Reaction Scheme I, an N-oxide of Formula XIV is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of the Formula XV. The reaction is carried out in two parts. In part (i) a compound of Formula XV is reacted with an acylating agent. Suitable acylating agents include alkyl- or arylsulfonyl chlorides (e.g., benzenesulfonyl chloride, methanesulfonyl chloride, and *p*-toluenesulfonyl chloride). In part (ii) the product of part (i) is reacted with an excess of an aminating agent. Suitable aminating agents include ammonia (e.g. in the form of ammonium hydroxide) and ammonium salts (e.g., ammonium carbonate, ammonium bicarbonate, ammonium phosphate). The reaction can be carried out by dissolving a compound of Formula XIV in a suitable solvent such as dichloromethane, adding ammonium hydroxide to the solution, and then adding *p*-toluenesulfonyl chloride.

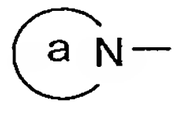
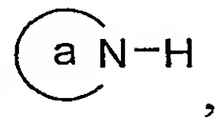
Alternatively, in step (4) the oxidation of step (4a) and the amination of step (4b) can be carried out sequentially without isolating the product of the oxidation to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of the Formula XV. In step (4), after the 1*H*-imidazo compound of Formula XIII is consumed by reaction with 3-chloroperoxybenzoic acid as described in step (4a), the aminating and acylating agents are added to the reaction mixture as in step (4b).

In step (5) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of the Formula XV is subjected to a copper-catalyzed amination with a nitrogen-containing heterocyclyl compound of the Formula  wherein  is defined above, to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula IIc. Many of these nitrogen-containing heterocyclyl compounds are commercially available; others can be prepared by known methods. The reaction is carried out by combining the 1*H*-imidazo[4,5-*c*]quinolin-4-amine of the Formula XV and the nitrogen-containing heterocyclyl compound in the presence of copper (I) iodide, potassium phosphate, and racemic *trans*-1,2-diaminocyclohexane in a suitable solvent such as 1,4-dioxane. The reaction can be carried out at an elevated temperature such as 110 °C. The compound or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme I

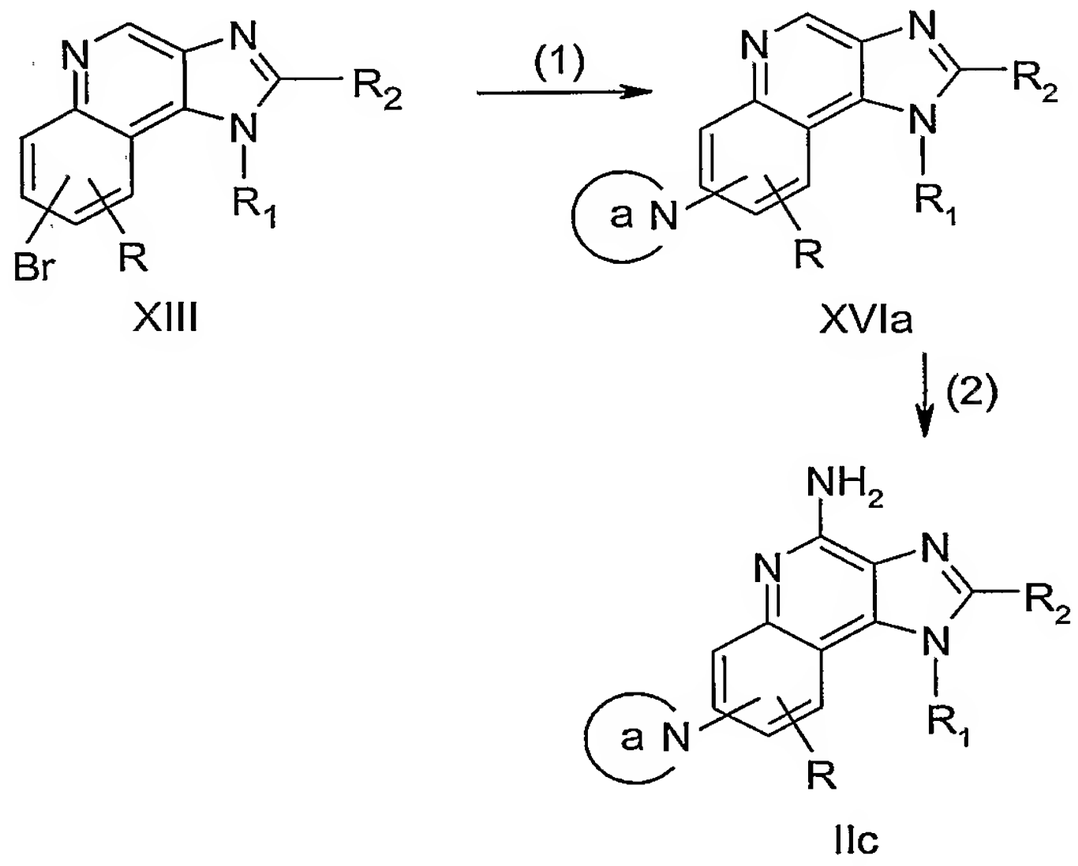


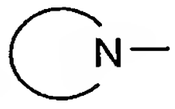
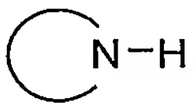
Many compounds of the Formula XV are known and can be used in Reaction Scheme I at step (5). See, for example, U.S. Patent Nos. 4,689,338; 4,929,624; 5,268,376; 5,346,905; 5,389,640; 5,756,747; 6,331,539; 6,451,810; 6,541,485; 6,677,349; 6,660,747; 6,670,372; 6,683,088; 6,656,938; 6,664,264; 6,664,260; European Patent Application 1 104 764; and Japanese Patent Application 9-255926. Others can be readily prepared using known synthetic methods. See, for example, U.S. Patent Nos. 4,988,815; 5,175,296; 5,367,076; 5,395,937; and 5,741,908.

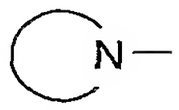
Compounds of the invention can be also prepared according to Reaction Scheme II wherein R, R_1, R_2, and  are as defined above. In step (1) of Reaction Scheme II, a 1*H*-imidazo compound of the Formula XIII is subjected to a copper-catalyzed amination with a nitrogen-containing heterocyclyl compound of the Formula  , as described in step (5) of Reaction Scheme I, to provide a 1*H*-imidazo compound of Formula XVIa

In step (2) of Reaction Scheme II, a 1*H*-imidazo compound of Formula XVIa is oxidized to provide an *N*-oxide which is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula IIc. The reaction is carried out as in steps (4a) and (4b) or step (4) of Reaction Scheme I. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme II



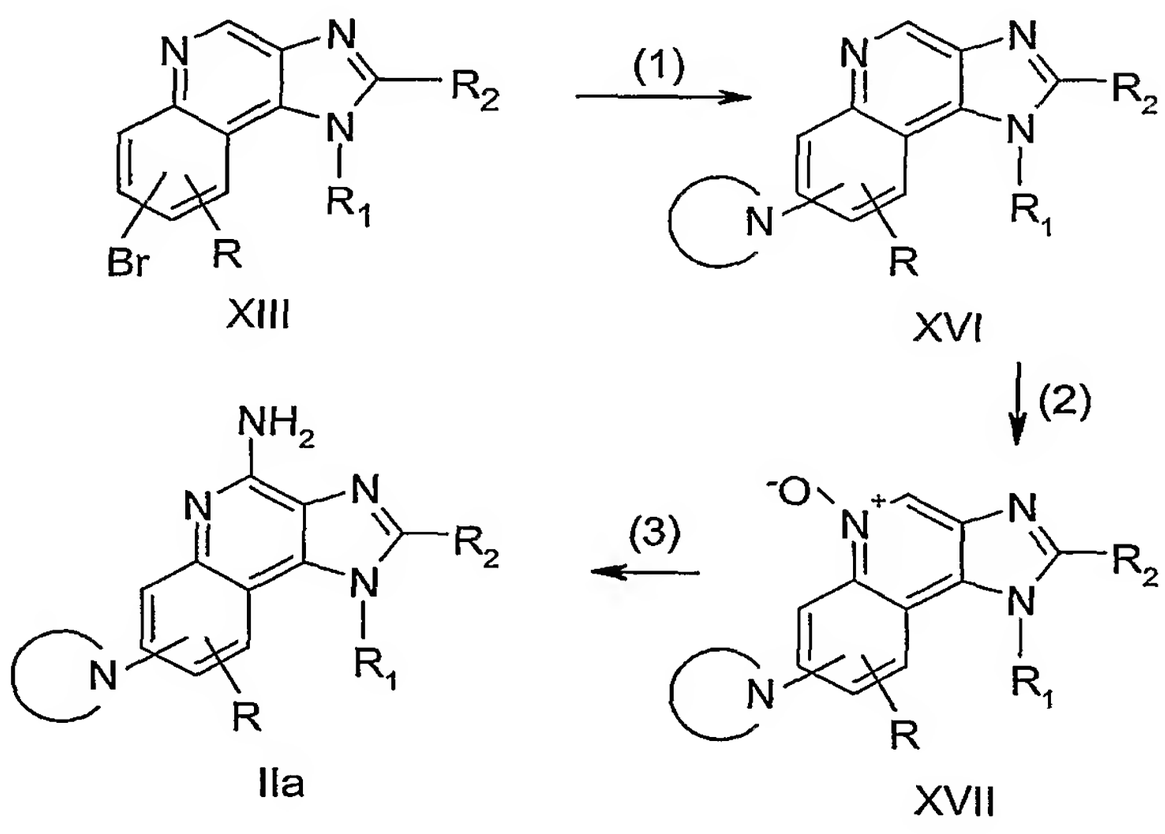
Compounds of the invention can be also prepared according to Reaction Scheme III wherein R, R_1, R_2, and  are as defined above. In step (1) of Reaction Scheme III, a 1*H*-imidazo compound of the Formula XIII is subjected to a palladium-catalyzed amination with a nitrogen-containing heterocyclyl compound of the Formula  ,

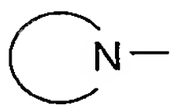
wherein  is as described above, to provide a 1*H*-imidazo compound of Formula XVI. Many of these nitrogen-containing heterocyclyl compounds are commercially available; others can be prepared by known methods. The reaction is carried out by combining the 1*H*-imidazo compound of the Formula XIII and the nitrogen-containing heterocyclyl compound in the presence of tris(dibenzylideneacetone)dipalladium, (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, sodium *tert*-butoxide, and a suitable solvent such as toluene. The reaction can be carried out at an elevated temperature such as 80 °C.

In step (2) of Reaction Scheme III, a 1*H*-imidazo compound of Formula XVI is oxidized to provide a 5*N*-oxide of Formula XVII. The reaction is carried out by combining the 1*H*-imidazo compound of Formula XVI with benzonitrile and sodium bicarbonate in a suitable solvent such as methanol, and then slowly adding hydrogen peroxide (55% by weight in water). The reaction can be carried out at room temperature.

In step (3) of Reaction Scheme III, a 5*N*-oxide of Formula XVII is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of the Formula IIa. The reaction can be carried out as in step (4b) of Reaction Scheme I. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme III



Compounds of the invention can be also prepared according to Reaction Scheme IV wherein R, R_1, R_2, and  are as defined above and E is a carbon atom or a nitrogen atom. Scheme IV begins with a bromo aniline or bromo aminopyridine of Formula XVIII, many of which are commercially available or can be prepared using conventional synthetic methods. In step (1) of Reaction Scheme IV, a bromo aniline or bromo aminopyridine of Formula XVIII is treated with the condensation product generated from 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) and triethyl orthoformate to provide an imine of Formula XIX. The reaction is conveniently carried out by adding a bromo aniline or bromo aminopyridine of Formula XVIII to a heated mixture of Meldrum's acid and triethyl orthoformate and heating the reaction at an elevated temperature such as 55 °C.

In step (2) of Reaction Scheme IV, an imine of Formula XIX undergoes thermolysis and cyclization to provide a compound of Formula XX. The reaction is carried out in a medium such as DOWTHERM A heat transfer fluid at a temperature between 200 and 250 °C.

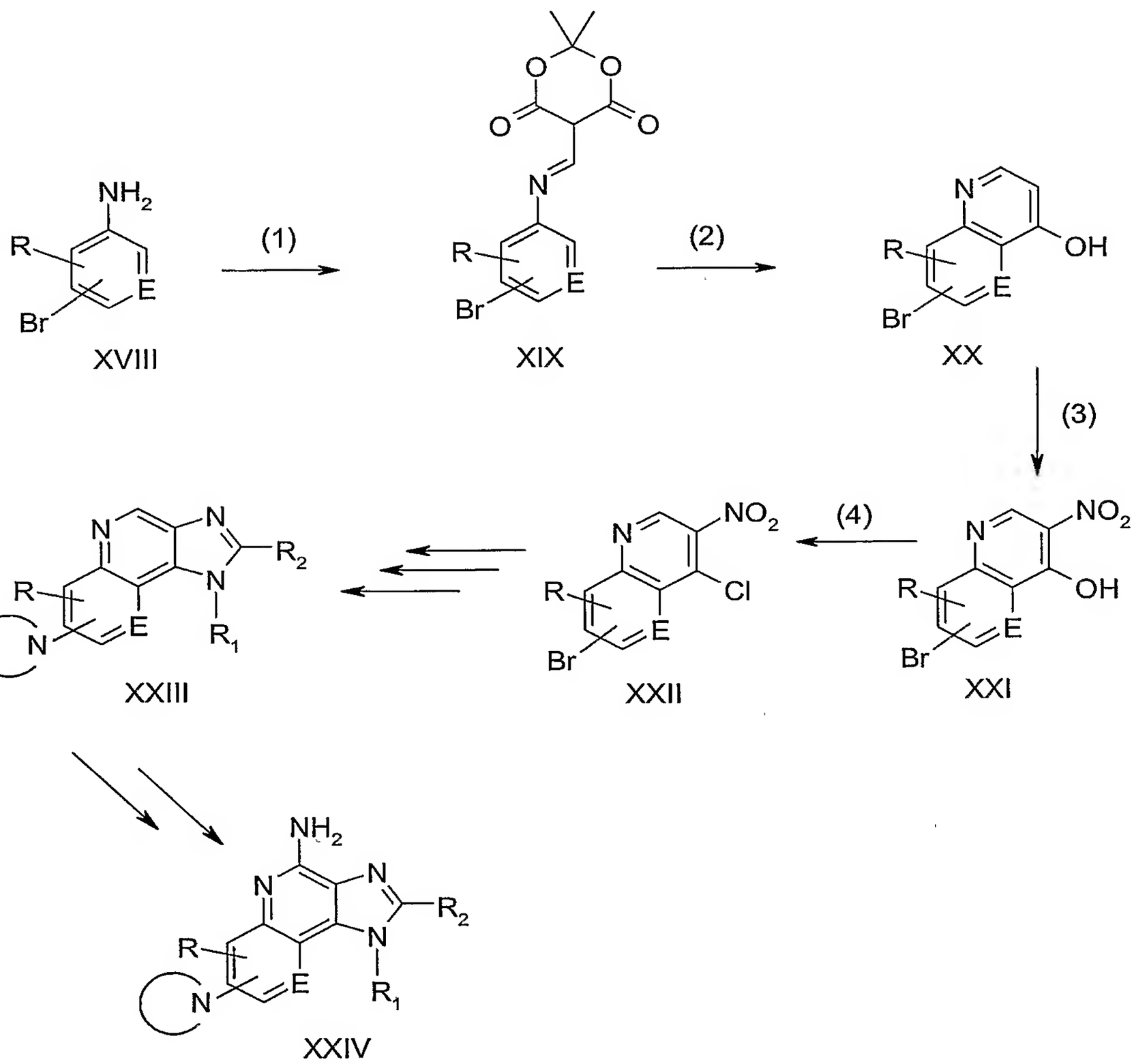
In step (3) of Reaction Scheme IV, a compound of Formula XX is nitrated under conventional nitration conditions to provide a compound of Formula XXI. The reaction is carried out by combining a compound of Formula XX with fuming nitric acid and heating the mixture at an elevated temperature such as 90 °C.

In step (4) of Reaction Scheme IV, a compound of Formula XXI is chlorinated using conventional methods to provide a compound of Formula XXII. The reaction is carried out by adding phosphorous oxychloride to a suspension of a compound of Formula XXI in a suitable solvent such as *N,N*-dimethylformamide. The reaction can be carried out at ambient temperature.

A compound of Formula XII is converted to a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXIII using the methods of steps (1) through (3) of Reaction Scheme I.

A 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXIII can be converted to a 1*H*-imidazo[4,5-*c*]quinolin-4-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine of Formula XXIV using the methods described in Reaction Schemes I, II, and III.

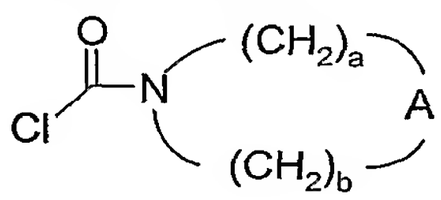
Reaction Scheme IV



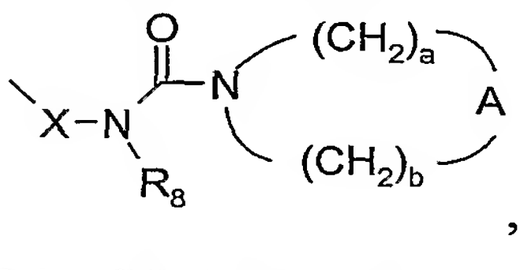
Compounds shown in Reaction Scheme I can be further elaborated using conventional synthetic methods. For example, an amine of Formula R_1-NH_2 may be substituted by a hydroxy or second amino group, which may be further functionalized before step (2) of Reaction Scheme I. For example, a 3-nitroquinolin-4-amine of Formula XI, in which R_1 is has an amino substituent, can be reacted with an acid chloride of Formula $R_{4b}C(O)Cl$, a sulfonyl chloride of Formula $R_{4b}S(O)_2Cl$, or a sulfonic anhydride of Formula $(R_{4b}S(O)_2)_2O$ to provide a compound of Formula XI in which R_1 is -X-Y-R_{4b}, where Y is -N(R_8)-Q-, R_8 is as defined above, Q is -C(O)- or -SO_2-, and R_{4b} is a subset of R_4 that does not include those substitutents which one skilled in the art would recognize as being susceptible to oxidation in step (4a). Numerous acid chlorides, sulfonyl chlorides, and sulfonic anhydrides are commercially available; others can be readily prepared using

known synthetic methods. The reaction can be conveniently carried out by adding an acid chloride of Formula $R_{4b}C(O)Cl$, a sulfonyl chloride of Formula $R_{4b}S(O)_2Cl$, or a sulfonic anhydride of Formula $(R_{4b}S(O)_2)_2O$ to a solution of a 3-nitroquinolin-4-amine of Formula XI, in which R_1 has an amino substituent, and a base such as triethylamine in a suitable solvent such as dichloromethane. The reaction can be carried out at ambient temperature.

A 3-nitroquinolin-4-amine of Formula XI, in which R_1 is has an amino substituent, can also react with isocyanates of Formula $R_{4b}N=C=O$ to provide a compound of Formula XI in which R_1 is $-X-Y-R_{4b}$, where Y is $-N(R_8)-Q-$, R_8 is as defined above, and Q is $-C(R_6)-N(R_8)-W-$, R_6 is =O, and W is a bond. Numerous isocyanates of Formula $R_{4b}N=C=O$ are commercially available; others can be readily prepared using known synthetic methods. The reaction can be conveniently carried out by adding the isocyanate of Formula $R_{4b}N=C=O$ to a solution of the 3-nitroquinolin-4-amine of Formula XI, in which R_1 has an amino substituent, in a suitable solvent such as dichloromethane. The reaction can be carried out at ambient temperature. Alternatively, a compound of Formula XI, in which R_1 has an amino substituent, can be treated with an isocyanate of Formula $R_{4b}(CO)N=C=O$, a thioisocyanate of Formula $R_{4b}N=C=S$, a sulfonyl isocyanate of Formula $R_{4b}S(O)_2N=C=O$, or a carbamoyl chloride of Formula $R_{4b}N-(R_8)-C(O)Cl$ or



to provide a compound of Formula XI, where R_1 is $-X-N(R_8)-Q-R_{4b}$ or



Q is $-C(R_6)-N(R_8)-W-$, and R_6, R_8, and W are as defined above. The product can then be treated according to steps (2) through (5) of Reaction Scheme I to provide 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula IIc.

Several examples of synthetic elaborations of an R_1 group are known. See, for example, U.S. Patent Nos. 4,689,338 (Gerster), 4,929,624 (Gerster et al.), 5,268,376 (Gerster), 5,389,640 (Gerster et al.), 6,331,539 (Crooks et al.), 6,451,810 (Coleman et al.), 6,541,485 (Crooks et al.), 6,660,747 (Crooks et al.), 6,670,372 (Charles et al.), 6,683,088

(Crooks et al.), 6,656,938 (Crooks et al.), 6,664,264 (Dellaria et al.), and PCT Publication No. WO 03/103584.

Similar synthetic transformations can be made at R_2 if, for example, the acid chloride used in step (3) of Reaction Scheme I contains a protected hydroxy or amino group. Several acid chlorides of this type, for example acetoxyacetyl chloride, are commercially available. Others can be prepared by known synthetic methods. For examples of synthetic elaborations of an R_2 group, see U.S. Patent No. 5,389,640 (Gerster et al.).

Compounds of the invention can also be prepared using the synthetic routes described in the EXAMPLES below.

Prodrugs can be prepared in a variety of ways. For example, a compound wherein R_2 (or R_1) is -X-OH (e.g. hydroxyalkylenyl) can be converted into a prodrug wherein R_2 (or R_1) is, for example, -X-O-C(R_6)-R_4, -X-O-C(R_6)-O-R_4, or -X-O-C(R_6)-N(R_8)-R_4, wherein X, R_4, R_6, and R_8 are as defined above, using methods known to one skilled in the art. For any of these compounds containing an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as C_{1-6} alkanoyloxymethyl, 1-(C_{1-6} alkanoyloxy)ethyl, 1-methyl-1-(C_{1-6} alkanoyloxy)ethyl, C_{1-6} alkoxycarbonyloxymethyl, *N*-(C_{1-6} alkoxycarbonyl)aminomethyl, succinoyl, C_{1-6} alkanoyl, α-aminoC_{1-4} alkanoyl, arylacyl, -P(O)(OH)$_2$, -P(O)(O-C_{1-6} alkyl)$_2$, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbamoyl, and α-aminoacyl or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from racemic, D-, and L-amino acids. For compounds containing an alcohol functional group, particularly useful prodrugs are esters made from carboxylic acids containing one to six carbon atoms, unsubstituted or substituted benzoic acid esters, or esters made from racemic, D- or L-amino acids.

Prodrugs can also be made from a compound containing an amino group by conversion of the amino group to a functional group such as an amide, carbamate, urea, amidine, or another hydrolizable group using conventional methods. A prodrug of this type can be made by the replacement of a hydrogen atom in an amino group, particularly the amino group at the 4-position, with a group such as -C(O)-R'", α-aminoacyl, α-aminoacyl-α-aminoacyl, -C(O)-O-R'", -C(O)-N(R'")-R'", –C(=NY')-R'",

-CH(OH)-C(O)-OY', -CH(OC_{1-4} alkyl)Y_0, -CH_2Y_1, or -CH(CH_3)Y_1; wherein R''' and R'''' are each independently C_{1-10} alkyl, C_{3-7} cycloalkyl, or benzyl, each of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, arylC_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl, haloC_{1-4} alkyl, haloC_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and -$S(O)_2$-NH_2; each α-aminoacyl group is independently selected from racemic, D-, and L-amino acids; Y' is hydrogen, C_{1-6} alkyl, or benzyl; Y_0 is C_{1-6} alkyl, carboxyC_{1-6} alkylenyl, aminoC_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylaminoC_{1-4} alkylenyl, or di-*N,N*-C_{1-6} alkylaminoC_{1-4} alkylenyl; and Y_1 is mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, or 4-C_{1-4} alkylpiperazin-1-yl; with the proviso that R'''' can also be hydrogen.

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound or salt of the invention as described above in combination with a pharmaceutically acceptable carrier.

The terms “a therapeutically effective amount” and "effective amount" mean an amount of the compound or salt sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. Although the exact amount of active compound or salt used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μg/kg) to about 5 mg/kg, of the compound or salt to the subject. A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like.

The compounds or salts of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts of the invention may

be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compounds or salts of the invention have been shown to induce, and certain compounds or salts of the invention may inhibit, the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds or salts are useful as immune response modifiers that can modulate the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds or salts of the invention generally include interferon-α (IFN-α) and/or tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds or salts of the invention include IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds or salts useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. The animal to which the compound or salt or composition is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds or salts of the invention can affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds or salts may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, the compounds or salts may cause proliferation and differentiation of B-lymphocytes.

Compounds or salts of the invention can also have an effect on the acquired immune response. For example, the production of the T helper type 1 (T_H1) cytokine IFN-

γ may be induced indirectly and the production of the T helper type 2 (T_H2) cytokines IL-4, IL-5 and IL-13 may be inhibited upon administration of the compounds or salts.

Other cytokines whose production may be inhibited by the administration of compounds or salts of the invention include tumor necrosis factor-α (TNF-α). Among other effects, inhibition of TNF-α production can provide prophylaxis or therapeutic treatment of TNF-α mediated diseases in animals, making the compounds or salt useful in the treatment of, for example, autoimmune diseases. Accordingly, the invention provides a method of inhibiting TNF-α biosynthesis in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. The animal to which the compound or salt or composition is administered for inhibition of TNF-α biosynthesis may have a disease as described *infra*, for example an autoimmune disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or salt or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound or salt and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which compounds or salts identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B

virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carnii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, leukemias including but not limited to myelogeous leukemia, chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

(e) T_H2-mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

(f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

(g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

Additionally, a compound or salt of the present invention may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens; toxoids; toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B,

parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

Compounds or salts of the present invention may be particularly helpful in individuals having compromised immune function. For example, compounds or salts may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of the invention to the animal.

An amount of a compound or salt effective to induce or inhibit cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12 that is increased (induced) or decreased (inhibited) over a background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. An amount of a compound or salt effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected

to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg.

In addition to the formulations and uses described specifically herein, other formulations, uses, and administration devices suitable for compounds of the present invention are described in, for example, International Publication Nos. WO 03/077944 and WO 02/036592, U.S. Patent No. 6,245,776, and U.S. Publication Nos. 2003/0139364, 2003/185835, 2004/0258698, 2004/0265351, 2004/076633, and 2005/0009858.

EXAMPLES

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

Preparation of 7-Bromo-4-chloro-3-nitroquinoline

Part A

A mixture of triethyl orthoformate (154 grams (g), 1.04 moles (mol) and Meldrum's acid (142 g, 0.983 mol) was heated to 55°C for 4 hours (h). After cooling to 50°C, a solution of 3-bromoaniline (162.6 g, 0.945 mol) in ethanol (300 mL) was added such that the temperature of the reaction was maintained between 50-55°C. After half of the 3-bromoaniline had been added, stirring became difficult due to the formation of solids, so more ethanol (1 liter (L)) was added to facilitate stirring. Upon complete addition, the reaction was cooled to room temperature (RT), and the solids were collected by filtration. The filter cake was washed with ice cold ethanol until the washings were nearly colorless, and the product was dried at 65°C under vacuum to afford 287 g of 5-[(3-bromophenylamino)methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.19 (brd, J = 12.8 Hz, 1H), 8.60 (d, J = 14.0 Hz, 1H), 7.44-7.38 (m, 2H), 7.30 (t, J = 8.0 Hz, 1H), 7.18 (ddd, J = 8.0, 2.2, 0.9 Hz, 1H), 1.75 (s, 6H).

Part B

7-Bromoquinolin-4-ol was prepared in accordance with the literature procedure (D. Dibyendu et al., *J. Med. Chem.*, *41*, 4918-4926 (1998)) or by thermolysis of 5-[(3-bromophenylamino)methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione in DOWTHERM A heat transfer fluid and had the following spectral properties:

^{1}H NMR (300 MHz, d_6-DMSO) δ 11.70 (brs, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.92 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 1.9 Hz, 1H), 7.44 (dd, J = 8.7, 1.9 Hz, 1H), 6.05 (d, J = 7.5 Hz, 1H).

Part C

A stirred suspension of 7-bromoquinolin-4-ol (162 g, 0.723 mol) in propionic acid (1500 mL) was brought to 110°C. 70% Nitric acid (85 g) was added dropwise over 1 h such that the temperature was maintained between 110-115°C. After half of the nitric acid had been added, stirring became difficult due to the formation of solids and an additional 200 mL of propionic acid was added. Upon complete addition, the reaction was stirred for 1 h at 110°C, cooled to room temperature, and the solid was collected by filtration. The filter cake was washed with ice cold ethanol until the washings were nearly colorless (800 mL), and the product was dried at 60°C under vacuum to afford 152 g of 7-bromo-3-nitro-quinolin-4-ol as a pale yellow solid.

^{1}H NMR (300 MHz, d_6-DMSO) δ 13.0 (brs, 1H), 9.22 (s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 1.6 Hz, 1H), 7.66 (dd, J = 8.7, 1.9 Hz, 1H).

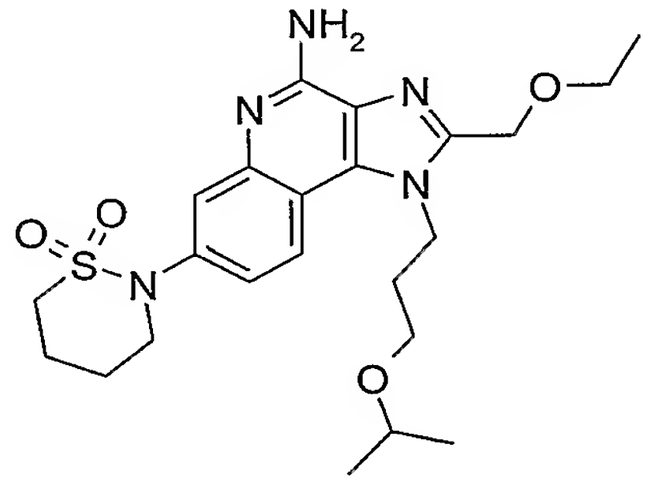
Part D

7-Bromo-3-nitroquinolin-4-ol (42 g, 156 millimoles (mmol)) was suspended in $POCl_3$ (130 mL) and brought to 102°C under an atmosphere of N_2. After 45 min, all of the solids had dissolved, so the reaction was cooled to room temperature (RT). The resulting solids were collected by filtration, washed with H_2O, and then partitioned with CH_2Cl_2 (3 L) and 2M Na_2CO_3 (500 mL). The organic layer was separated, washed with H_2O (1x), dried over Na_2SO_4, filtered, and concentrated to afford 33.7 g of 7-bromo-4-chloro-3-nitroquinoline as a beige solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.41 (d, J = 1.8 Hz, 1H), 8.30 (d, J = 9.0 Hz, 1H), 7.90 (dd, J = 8.9, 2.1 Hz, 1H).

Example 1

7-(1,1-Dioxo-[1,2]thiazinan-2-yl)-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

7-Bromo-4-chloro-3-nitroquinoline (40 g) was dissolved in dichloromethane (1.4 L) and triethylamine (23.3 mL). 3-Isopropoxypropylamine (19.3 mL) was added dropwise. After 48 hours, the reaction mixture was washed successively with water and saturated aqueous sodium chloride. The organic fraction was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. (7-Bromo-3-nitroquinolin-4-yl)-(3-isopropoxypropyl)amine was isolated as a tan solid (51.2g).

Part B

(7-Bromo-3-nitroquinolin-4-yl)-(3-isopropoxypropyl)amine (51 g) was slurried in acetonitrile (750 mL) and added to a Parr flask containing 5% platinum on carbon (5 g). The flask was degassed three times, then charged with hydrogen (30 psi) and shaken for 4 hours with replenishment of the hydrogen as necessary. The platinum catalyst was removed by filtration through a bed of CELITE filter agent. The filtrate was evaporated to afford 7-bromo-N^4-(3-isopropoxypropyl)quinoline-3,4-diamine as a yellow oil (45 g).

Part C

7-Bromo-N^4-(3-isopropoxypropyl)quinoline-3,4-diamine (45 g) was dissolved in acetonitrile (1.3 L) and triethylamine (19.4 mL). Ethoxyacetyl chloride (18.0 g) was added dropwise to the solution and the reaction was stirred for 16 hours. The solvent was removed under reduced pressure to afford a tan solid. The solid was added to a solution of ethanol (1 L) and triethylamine (77.5 mL) and heated at reflux for 4 hours. The solvent was removed under reduced pressure. Water was added to the solid residue and the crude product was recovered by filtration. Recrystallization from acetonitrile yielded 36.25 g of

7-bromo-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinoline as a tan crystalline solid.

Part D

7-Bromo-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinoline (20 g) was dissolved in chloroform (400 mL). 3-Chloroperoxybenzoic acid (60 % pure, 17.1 g) was added in 2 g portions over a 5 minute period and the reaction was stirred for 1 hour. Ammonium hydroxide (300 mL) was added and the mixture was cooled to 5 °C with an ice/water bath. *p*-Toluenesulfonyl chloride (9.4 g) was added at the rate of 1 g/min to minimize gas evolution. After stirring for 16 hours, the layers were separated and the aqueous fraction was extracted with chloroform. The combined organic fractions were sequentially washed with 5% aqueous sodium bicarbonate, water and brine; dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel. The polar component of the eluent was chloroform:methanol:ammonium hydroxide 80:18:2 (CMA). The purification was carried out eluting with chloroform:CMA in a gradient from 98:2 to 88:12. The material recovered from the column was recrystallized from acetonitrile to yield 7.0 g of 7-bromo-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a tan granular powder.

Part E

7-Bromo-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.75 g), 1,4-butanesultam (0.29 g), copper(I) iodide (68 mg), (±)-*trans*-1,2-diaminocyclohexane (42 µL), potassium phosphate (0.79 g) and dioxane (4 mL) were added to a scintillation vial. The vial was flushed with nitrogen, sealed with a Teflon-lined cap, placed in an oil bath, and heated at 110 °C for 30 hours. The reaction was cooled to ambient temperature, diluted with chloroform and filtered through a bed of CELITE filter agent. The solvent was evaporated and the residue was purified by column chromatography on a Biotage Horizon™ High-Performance Flash Chromatography instrument using a silica gel cartridge. The polar component of the eluent was chloroform:methanol:ammonium hydroxide 80:18:2 (CMA). The purification was carried out eluting with chloroform:CMA in a gradient from 99:1 to 90:10. Additional purification by recrystallization from acetonitrile provided 0.47 g of 7-(1,1-dioxo-

[1,2]thiazinan-2-yl)-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as pale yellow crystals, mp 172-174 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.17 (d, J = 8.8 Hz, 1H), 7.51 (d, J = 2.2 Hz, 1H), 7.18 (dd, J = 8.8, 2.2 Hz, 1H), 6.68 (s, 2H), 4.78 (s, 2H), 4.65-4.60 (m, 2H), 3.76-3.72 (m, 2H), 3.64-3.48 (m, 5H), 3.34-3.30 (m, 2H), 2.25-2.13 (m, 2H), 2.13-2.00 (m, 2H), 1.92-1.78 (m, 2H), 1.17 (t, J = 7.2 Hz, 3H), 1.15 (d, J = 6.0 Hz, 6H);

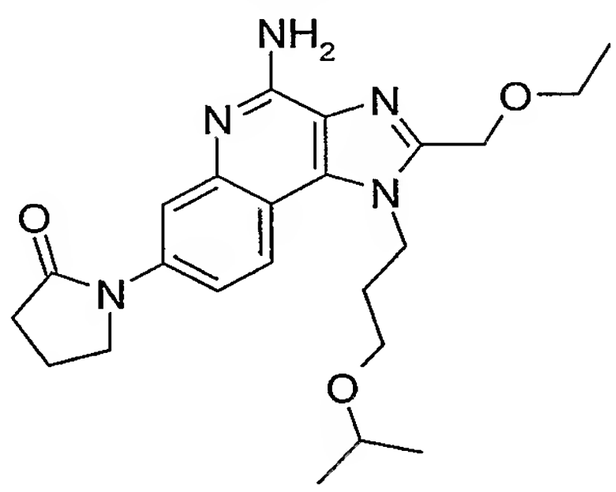
^{13}C NMR (75 MHz, DMSO-d_6) δ 152.4, 149.0, 145.6, 139.2, 132.7, 126.3, 123.0, 120.8, 120.2, 113.1, 70.8, 65.4, 64.1, 63.9, 53.2, 50.0, 42.9, 30.3, 23.9, 23.6, 22.0, 14.9;

MS (ESI) *m/z* 476.2336 (476.2332 calcd. for $C_{23}H_{33}N_5O_4S$, M+H);

Anal. Calcd. for $C_{23}H_{33}N_5O_4S$: %C, 58.08; %H, 6.99; %N, 14.72; %S, 6.74. Found: %C, 57.89; %H, 7.03; %N, 14.81; %S, 6.51.

Example 2

1-[4-Amino-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl] pyrrolidin-2-one



Part A

7-Bromo-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinoline (0.5 g), copper(I) iodide (0.046 g), (±)-*trans*-1,2-diaminocyclohexane (0.030 mL), 2-pyrrolidinone (0.122 mL), potassium phosphate (0.55 g) and dioxane (1.2 mL) were added to a 2 dram vial with a stir bar. The vial was flushed with nitrogen, sealed with a Teflon-lined cap, placed in an oil bath, and heated at 110 °C for 16 hours. The reaction was cooled to ambient temperature and then diluted with chloroform and water. The layers were separated and the aqueous fraction was extracted with chloroform. The combined organic fractions were sequentially washed with water and saturated aqueous sodium chloride; dried over anhydrous sodium sulfate; filtered and concentrated under reduced

pressure. The residue was purified by column chromatography on a Biotage Horizon™ High-Performance Flash Chromatography instrument using a silica gel cartridge. The polar component of the eluent was chloroform:methanol:ammonium hydroxide 80:18:2 (CMA). The purification was carried out eluting with chloroform:CMA in a gradient from 99:1 to 80:20. 1-[2-Ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]pyrrolidin-2-one was isolated as a yellow oil which solidified over time (0.38 g).

Part B

1-[2-Ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl] pyrrolidin-2-one (0.38 g) was dissolved in chloroform (10 mL). 3-Chloroperoxybenzoic acid (60% pure, 0.37 g) was added in one portion and the mixture was allowed to stir for 16 hours. Ammonium hydroxide (10 mL) was added and the biphasic mixture was cooled to 2 °C with an ice/water bath. Benzenesulfonyl chloride (0.22 mL) was added and the reaction was stirred for 3 hours. The layers were separated and the aqueous fraction was extracted with chloroform. The combined organic fractions were sequentially washed with water and saturated aqueous sodium chloride; dried over anhydrous sodium sulfate; filtered and concentrated under reduced pressure. The residue was purified by column chromatography on a Biotage Horizon™ High-Performance Flash Chromatography instrument using a silica gel cartridge. The polar component of the eluent was chloroform:methanol:ammonium hydroxide 80:18:2 (CMA). The purification was carried out eluting with chloroform:CMA in a gradient from 99:1 to 73:27. Fractions containing product were combined and concentrated under reduced pressure. The residue was recrystallized from acetonitrile to afford 0.14 g of 1-[4-amino-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]pyrrolidin-2-one as a white solid, mp 165-167 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.16 (d, J = 8.9 Hz, 1H), 7.76 (dd, J = 8.9, 2.3 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 6.58 (s, 2H), 4.76 (s, 2H), 4.64-4.59 (m, 2H), 3.93 (t, J = 7.0 Hz, 2H), 3.66-3.50 (m, 3H), 3.50 (t, J = 5.6 Hz, 2H), 2.56-2.50 (m, 2H), 2.15-2.02 (m, 4H), 1.17 (t, J = 7.0 Hz, 3H), 1.15 (d, J = 6.0 Hz, 6H);

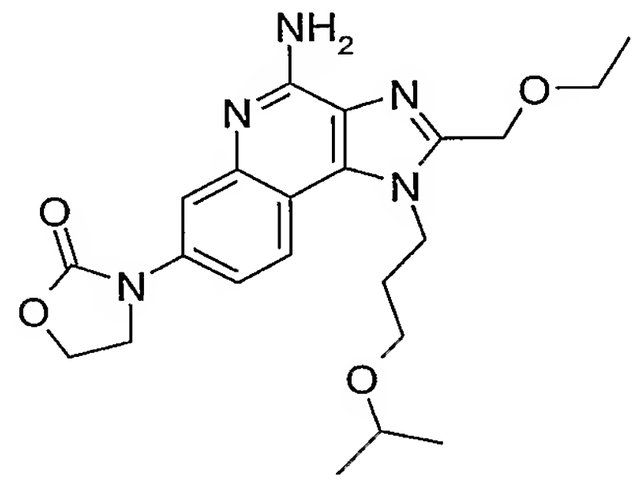
^{13}C NMR (75 MHz, DMSO-d_6) δ 173.9, 152.3, 148.6, 145.6, 138.4, 133.0, 125.7, 120.6, 115.3, 113.9, 110.9, 70.8, 65.4, 64.1, 63.9, 48.1, 42.8, 32.4, 30.3, 22.0, 17.4, 14.9;

MS (ESI) *m/z* 425.2506 (426.2505 calcd. for $C_{23}H_{31}N_5O_3$, M+H);

Anal. Calcd. for $C_{23}H_{31}N_5O_3$: %C, 64.92; %H, 7.34; %N, 16.46. Found: %C, 64.75; %H, 7.62; %N, 16.70.

Example 3

3-[4-Amino-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl] oxazolidin-2-one



The general methods described in Parts A and B of Example 2 were followed using 2-oxazolidinone in lieu of 2-pyrrolidinone. The product, 3-[4-amino-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]oxazolidin-2-one, was isolated as a white solid, mp 166-167 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.19 (d, J = 9.0 Hz, 1H), 7.67 (dd, J = 9.0, 2.3 Hz, 1H), 7.61 (d, J = 2.3 Hz, 1H), 6.61 (s, 2H), 4.76 (s, 2H), 4.65-4.60 (m, 2H), 4.50-4.45 (m, 2H), 4.19-4.14 (m, 2H), 3.64-3.48 (m, 5H), 2.13-2.02 (m, 2H), 1.17 (t, J = 7.0 Hz, 3H), 1.15 (d, J = 6.0 Hz, 6H);

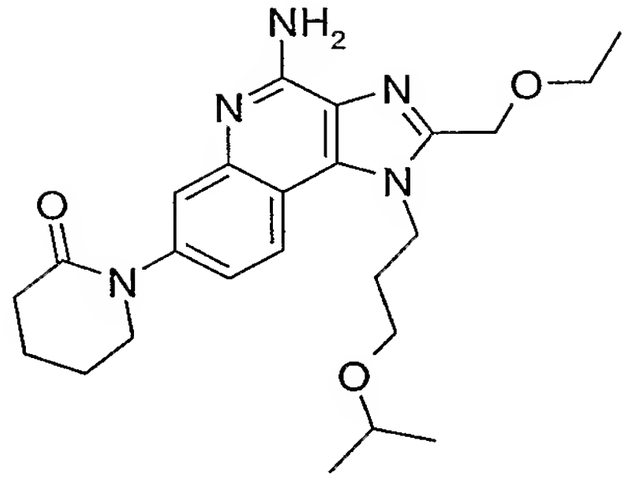
^{13}C NMR (125 MHz, DMSO-d_6) δ 154.9, 152.4, 148.6, 145.7, 137.3, 132.9, 125.7, 121.0, 113.9, 112.3, 110.6, 70.7, 65.3, 64.0, 63.8, 61.4, 44.7, 42.8, 30.3, 21.9, 14.8;

MS (ESI) *m/z* 428.2295 (428.2298 calcd. for $C_{22}H_{29}N_5O_4$, M+H);

Anal. Calcd. for $C_{22}H_{29}N_5O_4$: %C, 61.81; %H, 6.84; %N, 16.38. Found: %C, 61.62; %H, 6.84; %N, 16.34.

Example 4

1-[4-Amino-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl] piperidin-2-one



The general methods described in Parts A and B of Example 2 were followed using 2-piperidone in lieu of 2-pyrrolidinone. The product, 1-[4-amino-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]piperidin-2-one, was isolated as a yellow crystalline solid, mp 205-206.5 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.16 (d, J = 8.8 Hz, 1H), 7.45 (d, J = 2.1 Hz, 1H), 7.16 (dd, J = 8.7, 2.1 Hz, 1H), 6.63 (s, 2H), 4.77 (s, 2H), 4.66-4.61 (m, 2H), 3.71-3.67 (m, 2H), 3.64-3.48 (m, 5H), 2.45-2.41 (m, 2H), 2.15-2.02 (m, 2H), 1.96-1.80 (m, 4H), 1.17 (t, J = 7.0 Hz, 3H), 1.15 (d, J = 6.0 Hz, 6H);

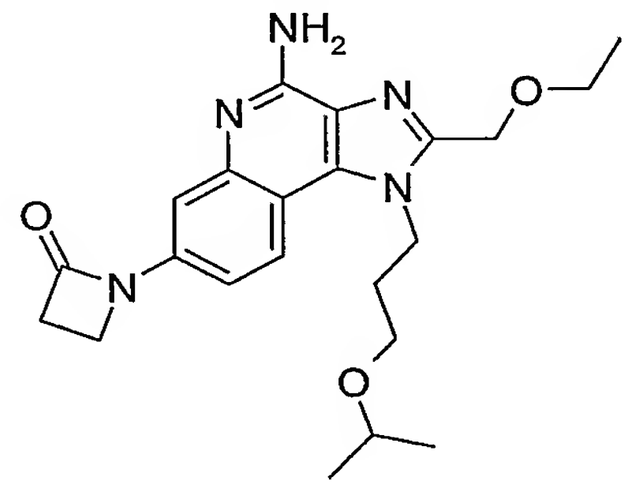
^{13}C NMR (75 MHz, DMSO-d_6) δ 168.8, 152.2, 148.9, 145.7, 142.4, 132.9, 126.1, 122.5, 120.5, 120.1, 112.6, 70.8, 65.4, 64.1, 63.9, 50.9, 42.9, 32.7, 30.3, 23.1, 22.0, 20.9, 14.9;

MS (ESI) *m/z* 440.2661 (440.2662 calcd. for $C_{24}H_{33}N_5O_3$, M+H);

Anal. Calcd. for $C_{24}H_{33}N_5O_3$: %C, 65.58; %H, 7.57; %N, 15.93. Found: %C, 65.34; %H, 7.80; %N, 15.92.

Example 5

1-[4-Amino-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl] azetidin-2-one



The general methods described in Parts A and B of Example 2 were followed using 2-azetidinone in lieu of 2-pyrrolidinone. The product, 1-[4-amino-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]azetidin-2-one, was isolated as a flocculent white solid, mp 185-186 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.16 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.39 (dd, J = 8.7, 2.2 Hz, 1H), 6.60 (s, 2H), 4.76 (s, 2H), 4.63-4.58 (m, 2H), 3.71 (t, J = 4.4 Hz, 2H), 3.64-3.48 (m, 5H), 3.11 (t, J = 4.3 Hz, 2H), 2.12-2.00 (m, 2H), 1.19-1.14 (m, 3H), 1.15 (d, J = 6.0 Hz, 6H);

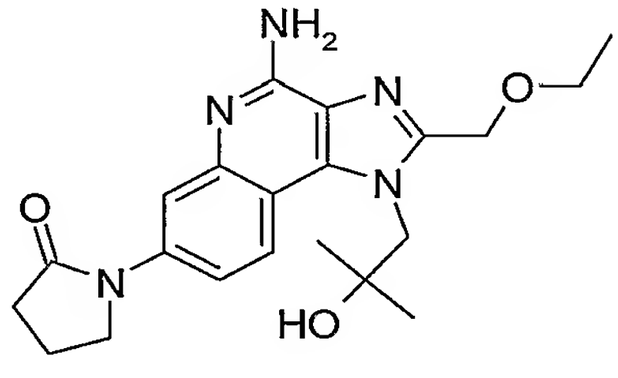
^{13}C NMR (125 MHz, DMSO-d_6) δ 164.7, 152.5, 148.5, 146.0, 137.3, 133.1, 125.5, 121.5, 111.2, 110.8, 110.7, 70.7, 65.3, 64.1, 63.9, 42.8, 37.9, 35.6, 30.3, 22.0, 14.9;

MS (ESI) *m/z* 412.2341 (412.2349 calcd. for $C_{22}H_{29}N_5O_3$, M+H);

Anal. Calcd. for $C_{22}H_{29}N_5O_3$: %C, 64.21; %H, 7.10; %N, 17.02. Found: %C, 63.98; %H, 7.38; %N, 17.07.

Example 6

1-[4-Amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]pyrrolidin-2-one



The general methods described in Parts A and B of Example 2 were followed using 1-(7-bromo-2-ethoxymethyl-1*H*- imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol in lieu of 7-bromo-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinoline. The product, 1-[4-amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]pyrrolidin-2-one, was isolated as a beige powder, mp 200-202 °C.

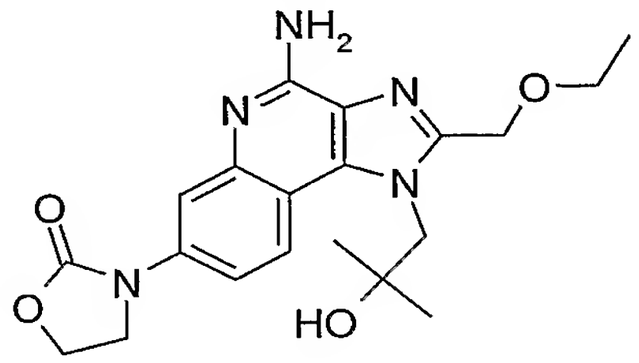
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.24 (d, J = 9.0 Hz, 1H), 7.74 (dd, J = 9.0, 2.3 Hz, 1H), 7.69 (d, J = 2.3 Hz, 1H), 6.55 (s, 2H), 5.0-4.8 (bs, 1H), 4.87 (s, 2H), 4.65 (bs, 2H), 3.92 (t, J = 7.0 Hz, 2H), 3.51 (q, J = 7.0 Hz, 2H), 2.56-2.50 (m, 2H), 2.14-2.04 (m, 2H), 1.17 (bs, 6H), 1.13 (d, J = 7.0 Hz, 3H);

MS (ESI) *m/z* 398.2193 (398.2192 calcd. for $C_{21}H_{27}N_5O_3$, M+H);

Anal. Calcd. for $C_{21}H_{27}N_5O_3$: %C, 63.46; %H, 6.85; %N, 17.62. Found: %C, 63.08; %H, 6.61; %N, 17.40.

Example 7

3-[4-Amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]oxazolidin-2-one



The general method described in Part E of Example 1 was followed using 1-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol and 2-oxazolidinone as reactants in lieu of 7-bromo-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine and 2-pyrrolidinone. The product, 3-[4-amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]oxazolidin-2-one, was isolated as a flocculent white solid, mp >250 °C.

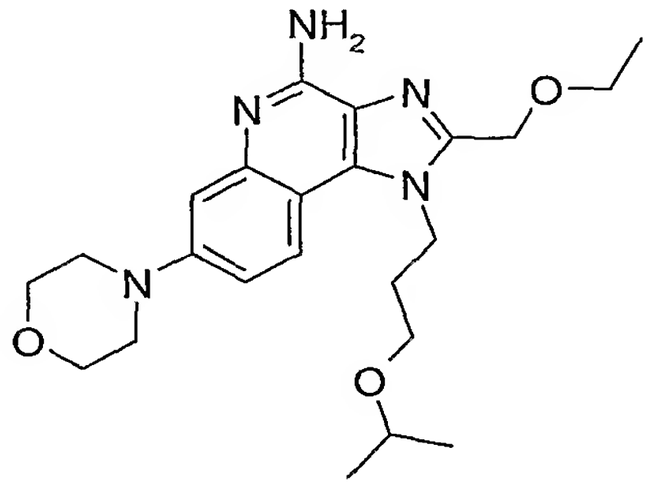
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.27 (d, J = 9.0 Hz, 1H), 7.64 (dd, J = 9.0, 2.5 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 6.56 (s, 2H), 5.02-4.77 (bs, 1H), 4.87 (s, 2H), 4.65 (bs, 2H), 4.50-4.44 (m, 2H), 4.18-4.13 (m, 2H), 3.51 (q, J = 7.0 Hz, 2H), 1.17 (bs, 6H), 1.13 (d, J = 7.0 Hz, 3H);

MS (ESI) *m/z* 400.1987 (400.1985 calcd. for $C_{20}H_{25}N_5O_4$, M+H);

Anal. Calcd. for $C_{20}H_{25}N_5O_4$: %C, 60.14; %H, 6.31; %N, 17.53. Found: %C, 59.88; %H, 6.19; %N, 17.36.

Example 8

2-Ethoxymethyl-1-(3-isopropoxypropyl)-7-(morpholin-4-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

7-Bromo-2-ethoxymethyl-1-(isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinoline (1.0 g), (±)-2,2'-bis(diphenylphosphino)-1,1'binaphthyl (BINAP, 0.089 g), tris(dibenzylideneacetone)dipalladium(0) (0.074 g), sodium tert-butoxide (0.320 g,), morpholine (0.230 mL,) and toluene (4.8 mL) were added to a scintillation vial. The vial was sequentially flushed with nitrogen, sealed with a Teflon-lined cap, placed in an oil bath, and heated at 80 °C for 16 hours. The reaction mixture was cooled to ambient temperature and then transferred to a round bottom flask. The volatiles were removed under reduced pressure and the residue was purified by column chromatography on a Biotage Horizon™ High Performance Flash Chromatography instrument using a silica gel cartridge. The purification was carried out eluting with chloroform:CMA in a gradient from 98:2 to 75:25. 2-Ethoxymethyl-1-(3-isopropoxypropyl)-7-(morpholin-4-yl)-1*H*-imidazo[4,5-*c*]quinoline was isolated as a red-orange oil (1.32 g).

Part B

2-Ethoxymethyl-1-(3-isopropoxypropyl)-7-(morpholin-4-yl)-1*H*-imidazo[4,5-*c*]quinoline (1.0 g), benzonitrile (0.44 mL) and sodium bicarbonate (0.15 g) were slurried in methanol. Hydrogen peroxide (55% by weight in water, 0.395 mL) was added dropwise over 1 hour. The reaction was stirred overnight. The methanol was removed under reduced pressure and the residue was purified by column chromatography on a Biotage Horizon™ High Performance Flash Chromatography instrument. The purification was carried out eluting with chloroform:CMA in a gradient from 98:2 to 75:25. 2-

Ethoxymethyl-1-(3-isopropoxypropyl)-7-(morpholin-4-yl)-1*H*-imidazo[4,5-*c*]quinoline 5-oxide was isolated as a yellow oil (0.166 g).

Part C

2-Ethoxymethyl-1-(3-isopropoxypropyl)-7-(morpholin-4-yl)-1*H*-imidazo[4,5-*c*]quinoline 5-oxide from Part B was dissolved in dichloromethane (4 mL). Ammonium hydroxide (2 mL) was added, followed by *p*-toluenesulfonyl chloride (0.074 g). The reaction was stirred for 24 hours. The layers were separated and the aqueous fraction was extracted with dichloromethane. The combined organic fractions were concentrated under reduced pressure to yield a yellow-brown oil. The oil was covered with diethyl ether and a precipitate formed. The solid was recovered by filtration and then dried to provide 0.085 g of 2-ethoxymethyl-1-(3-isopropoxypropyl)-7-(morpholin-4-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white powder, mp 161-162.5 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.03 (d, J = 9.7 Hz, 1H), 7.01-6.99 (m, 2H), 6.40 (s, 2H), 4.73 (s, 2H), 4.60-4.55 (m, 2H), 3.79-3.76 (m, 4H), 3.63-3.46 (m, 5H), 3.20-3.17 (m, 4H), 2.11-1.99 (m, 2H), 1.18-1.14 (m, 3H), 1.15 (d, J = 6.1 Hz, 6H);

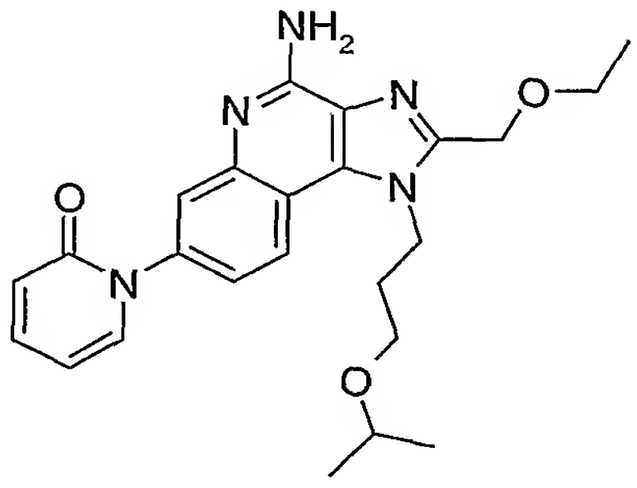
^{13}C NMR (125 MHz, DMSO-d_6) δ 152.0, 150.0, 147.8, 146.6, 133.4, 124.7, 121.0, 111.7, 109.7, 107.7, 70.7, 66.1, 65.2, 64.0, 63.8, 48.4, 42.6, 30.2, 21.9, 14.8;

MS (ESI) *m/z* 428.2655 (428.2662 calcd. for $C_{23}H_{33}N_5O_3$, M+H);

Anal. Calcd. for $C_{23}H_{33}N_5O_3$: %C, 64.61; %H, 7.78; %N, 16.38. Found: %C, 64.40; %H, 8.05; %N, 16.34.

Example 9

1-[4-Amino-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]-1*H*-pyridin-2-one



7-Bromo-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.75 g), 2(1*H*)-pyridone (0.20 g), copper(I) iodide (68 mg), *N,N'*-dimethylethylenediamine (75 μL), potassium phosphate (0.79 g) and dioxane (2.7 mL) were added to a scintillation vial. The vial was flushed with nitrogen, sealed with a Teflon-lined cap, placed in an oil bath, and heated to 110 °C for 60 hours. The reaction was cooled to ambient temperature, diluted with chloroform and filtered through a bed of CELITE filter agent. The solvent was evaporated and the residue was purified by column chromatography on a Biotage Horizon™ High-Performance Flash Chromatography instrument using a silica gel cartridge. The purification was carried out eluting with chloroform:CMA in a gradient from 99:1 to 75:25. Additional purification by recrystallization from acetonitrile provided 0.38 g of 1-[4-amino-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]-1*H*-pyridin-2-one as a tan solid, mp 161-163.5 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.30 (d, J = 8.8 Hz, 1H), 7.75 (dd, J = 6.8, 1.7 Hz, 1H), 7.56-7.50 (m, 2H), 7.24 (dd, J = 8.7, 2.2 Hz, 1H), 6.80 (s, 2H), 6.51 (d, J = 9.1 Hz, 1H), 6.36-6.31 (m, 1H), 4.80 (s, 2H), 4.70-4.65 (m, 2H), 3.64-3.49 (m, 5H), 2.17-2.03 (m, 2H), 1.18 (t, J = 7.0 Hz, 3H), 1.15 (d, J = 6.0 Hz, 6H);

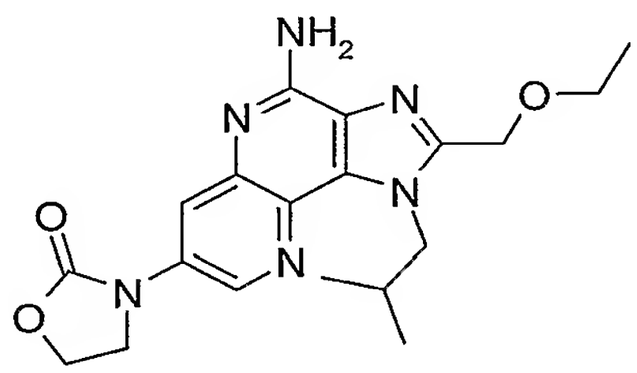
^{13}C NMR (75 MHz, DMSO-d_6) δ 161.3, 152.6, 149.3, 145.6, 140.5, 139.4, 139.2, 132.7, 126.6, 123.4, 121.0, 120.5, 119.7, 114.0, 105.5, 70.8, 65.5, 64.1, 63.9, 42.9, 30.3, 22.0, 14.9;

MS (APCI) *m/z* 436 $(M+H)^+$;

Anal. Calcd. for $C_{24}H_{29}N_5O_3$: %C, 66.19; %H, 6.71; %N, 16.08. Found: %C, 65.90; %H, 7.02; %N, 15.91.

Example 10

3-[4-Amino-2-ethoxymethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-7-yl]-1,3-oxazolidin-2-one



Part A

A mixture of triethyl orthoformate (10 mL, 60.1 mmol) and 2,2-dimethyl-[1,3]-dioxane-4,6-dione (40.9 g, 0.23 mol) (Meldrum's acid) was heated at 92 °C for 90 minutes and then cooled to 70 °C over one hour. 3-Amino-5-bromopyridine (40.9 g, 0.20 mol) was slowly added over 10 minutes with an ethanol rinse while maintaining the reaction temperature between 60 and 70 °C. The reaction was then heated for an additional 20 minutes and allowed to cool to room temperature. The reaction mixture was filtered and washed with ethanol (150 mL) yielding a tan solid. The solid was dried under vacuum for 2 hours to yield 59.14 g of 5-{[(5-bromopyridin-3-yl)imino]methyl}-2,2-dimethyl-1,3-dioxane-4,6-dione as a light yellow crystalline solid, mp 200-202 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.26 (d, J = 14.3 Hz, 1H), 8.80 (d, J = 2.3 Hz, 1H), 8.62 (d, J = 14.3 Hz, 1H), 8.56(d, J = 1.9 Hz, 1H), 8.44-8.40 (m, 1H), 1.68 (s, 6H).

Part B

5-{[(5-Bromopyridin-3-yl)imino]methyl}-2,2-dimethyl-1,3-dioxane-4,6-dione (59 g, 0.18 mol) was slowly added to DOWTHERM A heat transfer fluid (2000 mL) over a period of 5 minutes at 235-238 °C. Following addition, the reaction was maintained for an additional 5 minutes and then allowed to cool to 40 °C. A brown precipitate formed, which was filtered and washed with hexanes (150 mL). The brown solid was suspended in an ethanol/water mixture (90:10, 1500 mL), heated to a boil for 30 minutes, isolated by filtration, and washed with ethanol (200 mL) to yield 30.8 g of 7-bromo[1,5]naphthyridin-4-ol as a dark brown powder.

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.81(br s, 1H), 8.69(d, J = 1.9 Hz, 1H), 8.21 (d, J = 1.9 Hz, 1H), 7.95(d, J = 7.7 Hz, 1H), 6.22 (d, J = 7.5 Hz, 1H).

Part C

A mixture of 7-bromo[1,5]naphthyridin-4-ol (33 g, 0.147 mol) and fuming nitric acid (350 mL) was heated at reflux (90 °C internal reaction vessel temperature) for 3 hours. The reaction mixture was cooled to 50 °C, poured over 1 L of ice and neutralized to pH 2-3 with a solution of 50% aqueous NaOH. The resulting precipitate was filtered, washed with water, and dried over vacuum for 3 days to yield 25.1 g of 7-bromo-3-nitro[1,5]naphthyridin-4-ol as a yellow crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 13.06(br s, 1H), 9.26(s, 1H), 8.88 (d, J = 2.0 Hz, 1H), 8.37(d, J = 2.0 Hz, 1H).

Part D

Phosphorous oxychloride (16.76 g, 10.19 mL, 109.3 mmol) was added slowly dropwise to a suspension of 7-bromo-3-nitro[1,5]naphthyridin-4-ol (21.09 g, 78.1 mmol) in *N,N*-dimethylformamide (250 mL) (DMF) at ambient temperature and maintained overnight. The reaction mixture was then added to ice water (400 mL) with stirring. A solid precipitate formed, which was isolated by vacuum filtration and washed with water. The material was dried under high vacuum at ambient temperature overnight to yield 20.79 g of 7-bromo-4-chloro-3-nitro[1,5]naphthyridine as a tan solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51(s, 1H), 9.36 (d, J = 2.2 Hz, 1H), 9.02(d, J = 2.1 Hz,1H).

Part E

Triethylamine (17.97 mL, 129.0 mmol) was added to a solution of 7-bromo-4-chloro-3-nitro[1,5]naphthyridine (24.8 g, 86.0 mmol) in dichloromethane (200 mL) at 0 °C. Isobutylamine (9.40 mL, 94.6 mmol) was added dropwise to the mixture, and the mixture was stirred for 3 hours at ambient temperature. The reaction mixture was condensed under reduced pressure to a solid, which was triturated with water (200 mL). The precipitate was filtered, washed sequentially with water and hexanes, and dried to yield 27.5 g of 7-bromo-3-nitro[1,5]naphthyridin-4-yl-(2-methylpropyl)amine as a yellow powder, mp 114-115 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.98(br s, 1H), 9.37(br s, 1H), 8.81 (d, J = 2.2 Hz, 1H), 8.39(d, J = 2.2 Hz, 1H), 4.36-4.01(br m, 2H), 2.06(heptet, J = 6.7 Hz, 1H), 1.09(d, J = 6.7, 6H). MS (APCI) *m/z* 325.2 and 327.2 $(M+H)^+$;

Anal. calcd for $C_{12}H_{13}BrN_4O_2$: C, 44.33; H, 4.03; N, 17.23. Found: C, 44.32; H, 3.81; N, 17.33.

Part F

A solution of sodium dithionite (77.95 g, 380.6 mmol) and potassium carbonate (58.35 g, 422.2 mmol) in water (250 mL) was added dropwise to a mechanically stirred solution of 7-bromo-3-nitro[1,5]naphthyridin-4-yl-(2-methylpropyl)amine (27.6 g, 84.6 mmol) and ethyl viologen dibromide (0.63 g, 1.7 mmol) in dichloromethane (300 mL) and water (50 mL). The reaction mixture was stirred overnight at ambient temperature. Water (500 mL) was added, and the reaction mixture was stirred for 10 minutes. The organic layer was separated and the aqueous layer was filtered through WHATMAN paper to remove insoluble material. The emulsion-free filtrate was extracted with dichloromethane, washed sequentially with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield 22.3 g of 7-bromo-N^4-(2-methylpropyl)[1,5]naphthyridine-3,4-diamine as an orange solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, J = 2.2 Hz, 1H), 8.36(s, 1H), 8.33(d, J = 2.2 Hz, 1H), 6.03-5.89(br m, 1H), 3.66(br s, 2H), 3.27(t, J = 6.8, 2H), 1.83(heptet, J = 6.7 Hz, 1H), 1.00(d, J = 6.7 Hz, 6H). MS (APCI) *m/z* 295.1 and 297.1 $(M+H)^+$

Part G

A solution of 7-bromo-N^4-(2-methylpropyl)[1,5]naphthyridine-3,4-diamine (22.29 g, 75.51 mmol) in dichloromethane (300 mL) was cooled to 0 °C, and triethylamine (13.15 mL, 94.39 mmol) was added to the reaction mixture. Ethoxyacetyl chloride (11.56 g, 94.39 mmol) was added dropwise to the reaction mixture, and the reaction was maintained at ambient temperature for 2.5 hours. The reaction mixture was concentrated under reduced pressure, triethylamine (52.62 mL, 377.6 mmol) and ethanol (250 mL) was added, and the resulting mixture was heated at reflux for 16 hours. The solvent was removed under reduced pressure and the residue was triturated with *n*-heptanes. The resulting precipitate was collected by filtration, washed with water, and dried. The product was then recrystallized from acetonitrile to yield 14 g of 7-bromo-2-(ethoxymethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine as an off-white solid. The mother liquor was concentrated, and the residue was recrystallized from acetonitrile to yield an additional 2.37 g of 7-bromo-2-(ethoxymethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine. The *n*-heptanes fraction from the trituration was concentrated under

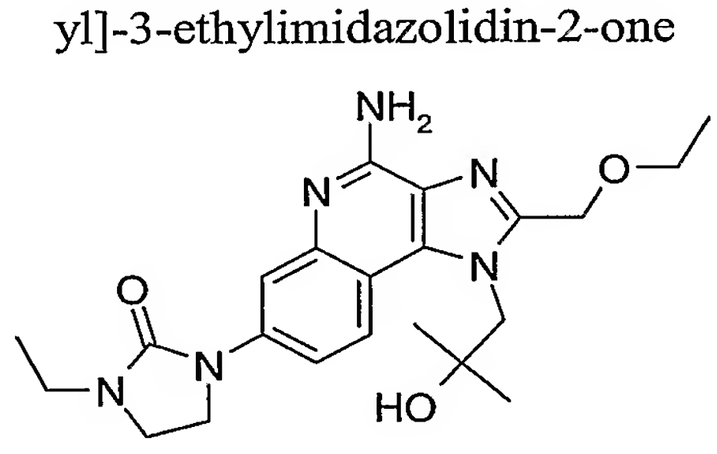
reduced pressure, triturated with acetonitrile, and isolated by filtration to give an additional 0.88 g of 7-bromo-2-(ethoxymethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine, for a total yield of 17.25 g of an off-white solid, mp 115-116 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.33(s, 1H), 8.96(d, J = 2.2 Hz, 1H), 8.68(d, J = 2.2 Hz, 1H), 4.90(s, 2H), 4.78(d, J = 7.6 Hz, 2H), 3.64(q, J = 7.0 Hz, 2H), 2.47(heptet, J = 6.9 Hz, 1H), 1.26(t, J = 7.0, 3H), 0.98(d, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 149.7, 147.2, 140.3, 139.3, 139.1, 134.5, 133.9, 117.9, 66.5, 65.3, 53.2, 29.7, 19.8, 15.0. Anal. calcd for $C_{16}H_{19}BrN_4O$: C, 52.90; H, 5.27; N, 15.42. Found: C, 52.93; H, 5.22; N, 15.55.

Part H

The general methods described in Parts A and B of Example 2 were followed using 7-bromo-2-(ethoxymethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine in lieu of 7-bromo-2-(ethoxymethyl)-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinoline and 2-oxazolidinone in lieu of 2-pyrrolidinone. The product, 3-[4-amino-2-ethoxymethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-7-yl]-1,3-oxazolidin-2-one (0.125 g) was isolated as an white solid with yellow tinge, m.p. 174-176.5 °C.
MS(ESI) m/z 385.1977 (385.1988 calcd. for $C_{19}H_{24}N_6O_3$, M+H);
Anal. Calcd. for $C_{19}H_{24}N_6O_3 \cdot 0.6H_2O$: %C, 57.74; %H, 6.43; %N, 21.26. Found: %C, 58.13; %H, 6.51; %N, 21.48.

Example 11

1-[4-Amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]-3-ethylimidazolidin-2-one



The general methods described in Parts A and B of Example 2 were followed using 1-(7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol in lieu of 7-bromo-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinoline and 1-

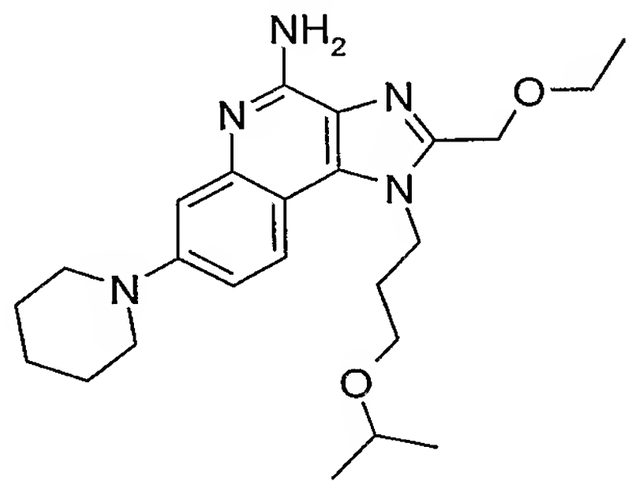
ethylimidazolidin-2-one in lieu of 2-pyrrolidinone. The product, 1-[4-amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]-3-ethylimidazolidin-2-one was isolated as a peach colored crystalline solid, m.p. 210-212 °C.

MS(ESI) m/z 427.2452 (427.2458 calcd. for $C_{22}H_{30}N_6O_3$, M+H);

Anal. Calcd. for $C_{22}H_{30}N_6O_3 \bullet 0.5H_2O$: %C, 60.67; %H, 7.18; %N, 19.30. Found: %C, 60.61; %H, 7.19; %N, 19.19.

Example 12

2-Ethoxymethyl-1-(3-isopropoxypropyl)-7-(piperidin-1-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

A slurry of 7-bromo-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinoline (6.6 g, 16.2 mmol) in ethyl acetate (55 mL) was heated to 50 °C. Peroxyacetic acid (5.12 mL, 24.4 mmol, of 32% in dilute acetic acid) was added dropwise over a period of 2 minutes. The reaction was allowed to stir at 50 °C for 2 hours. Additional peroxyacetic acid (1 mL) was added and the reaction mixture was stirred for an additional 2 hours. A solution of sodium metabisulfite (4.01 g, 21.1 mmol) in water (8 mL) was added. Following the addition of the sodium metabisulfite, the pH of the reaction mixture was adjusted to pH 10 with aqueous saturated sodium bicarbonate. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organics were washed sequentially with water and brine, dried over sodium sulfate, filtered, and then concentrated under reduced pressure to provide a yellow solid. This material was purified by flash chromatography (150 g of silica gel eluting with a

gradient of 1 – 12 % CMA in chloroform) to provide 5.49 g of 7-bromo-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinoline-5-oxide.

Part B

7-Bromo-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinoline-5-oxide (0.500 g), water (4.0 mL) , and piperidine (1.0 mL) were added sequentially to a 20 mL steel pressure vessel. The vessel was sealed and then heated in an oven at 150 °C for 16 hours. The reaction mixture was allowed to cool and then was extracted with chloroform (x2). The combined extracts were washed sequentially with water and brine and then dried over sodium sulfate. This material was combined with that from another run on the same scale and then purified by column chromatography on a Biotage Horizon™ High-Performance Flash Chromatography instrument using a silica gel cartridge and eluting with a gradient of 2 – 22 % CMA in chloroform to provide 0.137 g of 2-ethoxymethyl-1-(3-isopropoxypropyl)-7-(piperidin-1-yl)-1*H*-imidazo[4,5-*c*]quinoline-5-oxide as a brown oil.

Part C

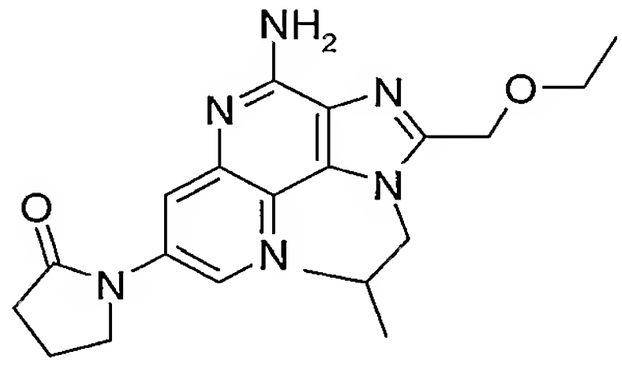
The material from Part B was dissolved in dichloromethane (5 mL). Ammonium hydroxide (2 mL) and *p*-toluenesulfonyl chloride (0.06 g, 0.32 mmol) were added sequentially. When analysis by thin layer chromatography indicated that the reaction was complete, the layers were separated. The organic layer was washed with brine, dried over sodium sulfate, filtered, and then concentrated under reduced pressure. This material was combined with that from another run and purified by column chromatography on a Biotage Horizon™ High-Performance Flash Chromatography instrument using a silica gel cartridge and eluting with a gradient of 2 – 25 % CMA in chloroform to provide an oil. The oil was triturated with acetonitrile to provide a solid which was isolated by filtration, washed with acetonitrile and dried under vacuum to provide 0.037 g of 2-ethoxymethyl-1-(3-isopropoxypropyl)-7-(piperidin-1-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as yellow crystals, m.p. 182.5-183.5 °C.

MS (ESI) *m/z* 426.54 $(M + H)^+$;

Anal. Calcd. for $C_{24}H_{35}N_5O_2$: %C, 67.74; %H, 8.29; %N, 16.46. Found: %C, 67.43; %H, 8.53; %N, 16.51.

Example 13

1-[4-Amino-2-ethoxymethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-7-yl]pyrrolidin-2-one



Part A

7-Bromo-2-(ethoxymethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine (1.0 g, 2.75 mmol), tris(dibenzylideneacetone)dipalladium(0) (70 mg, 0.068 mmol), cesium carbonate (1.25 g, 3.85 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.118 g, 0.204 mmol), pyrrolidin-2-one (0.25 mL, 3.3 mmol), and dioxane (2.75 mL) were added to a scintillation vial. The vial was sequentially flushed with nitrogen, sealed with a Teflon-lined cap, and heated at 110 °C for about 40 hours. After cooling to room temperature, the reaction mixture was diluted with chloroform and methanol and then filtered through CELITE filter aid. The filtrate was concentrated under reduced pressure to provide a tan solid. This material was purified by column chromatography on a Biotage Horizon™ High-Performance Flash Chromatography instrument using a silica gel cartridge and eluting with a gradient of 1 – 25 % CMA in chloroform to provide 1-[2-ethoxymethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-7-yl]pyrrolidin-2-one.

Part B

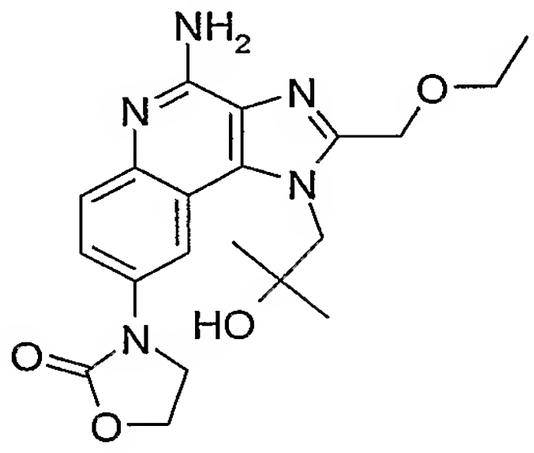
The material from Part A was oxidized and then aminated using the general method of Part B of Example 2 except that *p*-toluenesulfonyl chloride was used in lieu of benzenesulfonyl chloride. The crude product was purified by column chromatography on a Biotage Horizon™ High-Performance Flash Chromatography instrument using a silica gel cartridge and eluting with a gradient of 1 – 22 % CMA in chloroform followed by trituration with acetonitrile to provide 0.435 g of 1-[4-amino-2-ethoxymethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-7-yl]pyrrolidin-2-one as an off-white solid, m.p. 197.5-198.5 °C.

MS(ESI) m/z 383.2192 (383.2195 calcd. for $C_{20}H_{26}N_6O_2$, M+H);

Anal. Calcd. for $C_{20}H_{26}N_6O_2$: %C, 62.81; %H, 6.85; %N, 21.97. Found: %C, 62.52; %H, 6.92; %N, 21.71.

Example 14

3-[4-Amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-8-yl]-1,3-oxazolidin-2-one



Part A

8-Bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol (which can be prepared as described in US 2004/0147543, Examples 147-150) 0.550 g, 1.45 mmol), oxazolidin-2-one (0.151 g, 1.74 mmol), copper iodide (0.055 g), potassium phosphate (0.647 g, 3.05 mmol), dioxane (1.5 mL) and diaminocyclohexane (35 µL, 0.290 mmol) were added sequentially to a vial. The vial was flushed with nitrogen, sealed with a Teflon-lined cap, and heated at 110 °C over the weekend. The reaction mixture was allowed to cool and then it was diluted with dichloromethane (10 mL) and methanol (5 mL). The solution was purified by column chromatography on a Biotage Horizon™ High-Performance Flash Chromatography instrument using a silica gel cartridge and eluting with a gradient of 2 – 15 % CMA in chloroform to provide 0.38 g of 3-[2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-8-yl]-1,3-oxazolidin-2-one.

Part B

The material from Part A was oxidized and then aminated using the general method of Part B of Example 2 except that *p*-toluenesulfonyl chloride was used in lieu of benzenesulfonyl chloride. The crude product was purified by column chromatography on a Biotage Horizon™ High-Performance Flash Chromatography instrument using a silica gel cartridge and eluting with a gradient of 2 – 20 % CMA in chloroform followed by

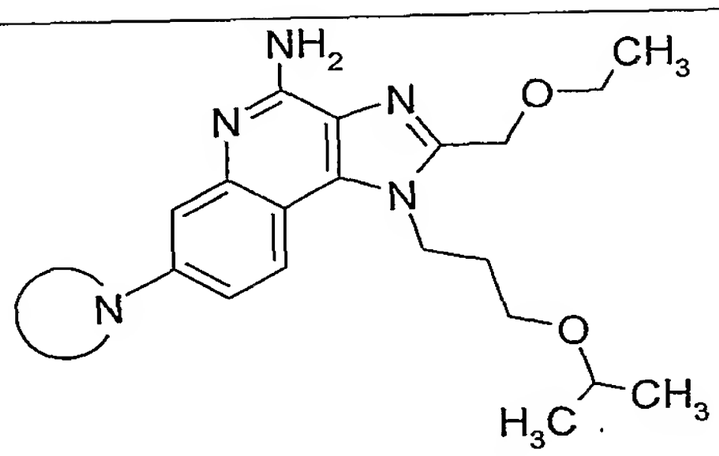
recrystallization from acetonitrile to provide 0.167 g of 3-[4-amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-8-yl]-1,3-oxazolidin-2-one as tan crystals, m.p. 207-209.5 °C.

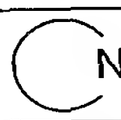
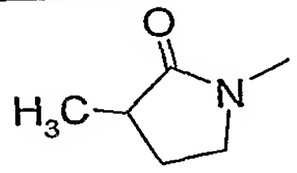
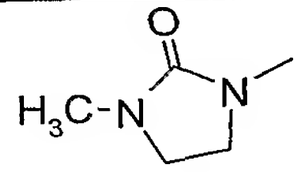
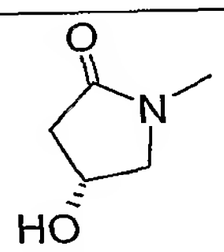
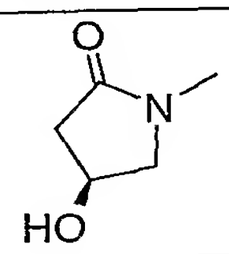
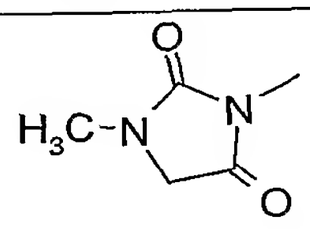
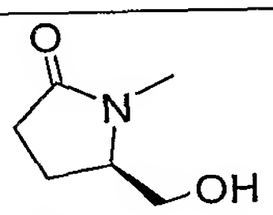
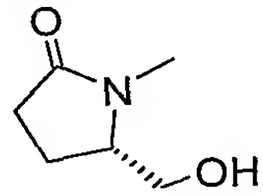
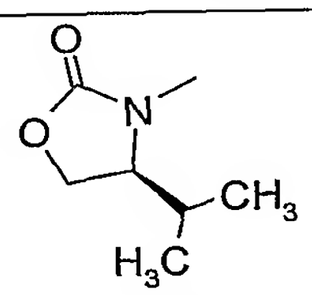
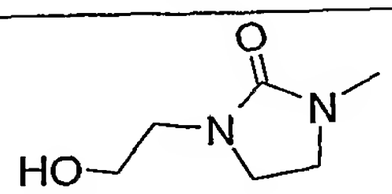
MS (APCI) *m/z* 400.15 $(M + H)^+$;

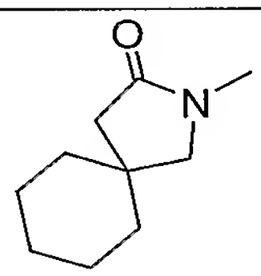
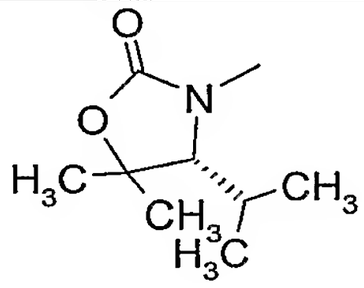
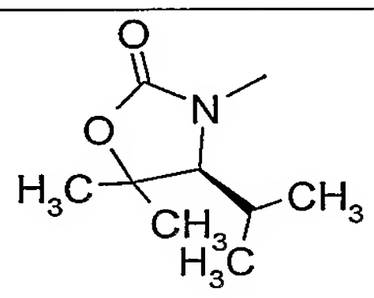
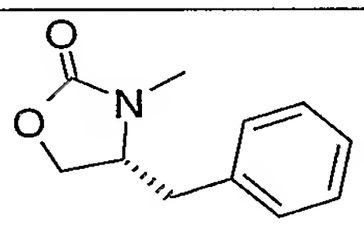
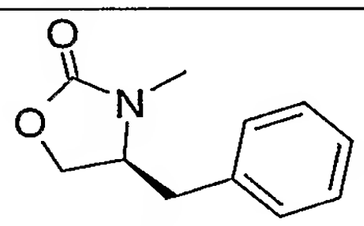
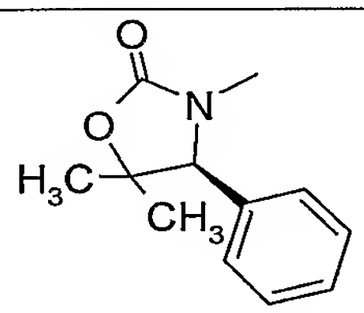
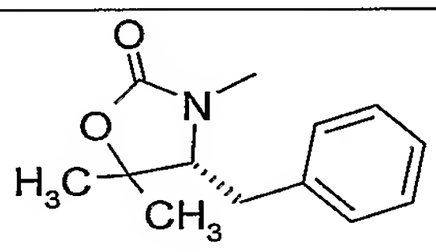
Anal. Calcd. for $C_{20}H_{25}N_5O_4$: %C, 60.14; %H, 6.31; %N, 17.53. Found: %C, 60.23; %H, 6.11; %N, 17.76.

Examples 15 – 30

A cyclic amide from the table below (1.2 eq) was added to a test tube containing 4 mg (0.2 eq) of copper iodide, 8 mg (2 eq) of potassium phosphate, and a magnetic stir bar. A solution of 7-bromo-2-ethoxymethyl-1-(3-isopropoxypropyl)-1*H*-imidazo[4,5-*c*]quinoline-4-amine (42 mg, 1.0 eq) in 1,4-dioxane (1.0 mL) was added to the test tube and the test tube was purged with nitrogen. *trans*-1,2-Diaminocyclohexane (4 µL, 0.3 eq) was added to the test tube and the test tube was purged with nitrogen. The test tube was capped and the reaction mixture was stirred at 110 °C overnight (about 16 hours). The test tube was cooled to ambient temperature and then charged with the appropriate cyclic amide, 4 mg (0.2 eq) of copper iodide, 8 mg (2 eq) of potassium phosphate, and *trans*-1,2-diaminocyclohexane (6 µL). The reaction mixture was stirred at 110 °C over the weekend. The reaction mixture was filtered and then concentrated by vacuum centrifugation. The compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters FractionLynx automated purification system. The prep HPLC fractions were analyzed using a Waters LC/TOF-MS, and the appropriate fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Reversed phase preparative liquid chromatography was performed with non-linear gradient elution from 5-95% B where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile. Fractions were collected by mass-selective triggering. The table below shows the cyclic amide used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



Example	Reagent		Measured Mass (M+H)
15	3-Methyl-2-pyrrolidinone		440.2621
16	1-Methyl-2-imidazolidinone		441.2594
17	(R)-(+)-4-Hydroxy-2-pyrrolidinone		442.2453
18	(*S*)-(-)-4-Hydroxy-2-pyrrolidinone		442.2434
19	1-Methylhydantoin		455.2408
20	(R)-(-)-5-(Hydroxymethyl)-2-pyrrolidinone		456.2632
21	L-Pyroglutaminol		456.2587
22	(*S*)-4-Isopropyl-2-oxazolidinone		470.2766
23	1-(2-Hydroxyethyl)-2-imidazolidinone		471.2715

24	4,4-Pentamethylene-2-pyrrolidinone		494.3153
25	(R)-(+)-4-Isopropyl-5,5-dimethyl-2-oxazolidinone		498.3062
26	(*S*)-(-)-4-Isopropyl-5,5-dimethyl-2-oxazolidinone		498.3059
27	(R)-4-Benzyl-2-oxazolidinone		518.2771
28	(*S*)-4-Benzyl-2-oxazolidinone		518.2739
29	(*S*)-Phenyl superquat		532.2928
30	(R)-(+)-4-Benzyl-5,5-dimethyl-2-oxazolidinone		546.3093

Examples 31 and 32

Part A

A mixture of 7-bromo-4-chloro-3-nitro[1,5]naphthyridine (92.5 g, 321 mmol) and dichloromethane (1.5 L) was cooled to 10 °C. 1-Amino-2-methylpropan-2-ol (63.01 g, 707 mmol) was added dropwise over a period of 30 minutes; during the addition, the reaction temperature did not rise above 13 °C. The reaction mixture was allowed to slowly warm to room temperature and stirred overnight. The solvent was removed under reduced pressure, and the solid residue was mixed with water (200 mL). The solid was

isolated by filtration, washed with water (2 x 200 mL), and dried in a vacuum oven overnight at 35 °C to provide 1-[(7-bromo-3-nitro[1,5]naphthyridin-4-yl)amino]-2-methylpropan-2-ol.

Part B

The material from Part A was added to a Parr vessel followed by methanol (1.13 L) and acetonitrile (2.26 L). The vessel was purged with nitrogen, and 5% platinum on carbon (3.4 g), which had been wet with acetonitrile, was added. The reaction mixture was placed under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) overnight and filtered. The filtrate was concentrated under reduced pressure to provide 103 g of 1-[(3-amino-7-bromo[1,5]naphthyridin-4-yl)amino]-2-methylpropan-2-ol as a yellow solid.

Part C

A mixture of 1-[(3-amino-7-bromo[1,5]naphthyridin-4-yl)amino]-2-methylpropan-2-ol (100.0 g, 321.4 mmol) and acetonitrile (1 L) was stirred for five minutes, and ethoxyacetyl chloride (43.3 g, 353.3 mmol) was added. The reaction was stirred overnight at room temperature. The solid product was isolated by filtration and washed with acetonitrile (200 mL) to provide 113 g of *N*-{7-bromo-4-[(2-hydroxy-2-methylpropyl)amino][1,5]naphthyridin-3-yl}-2-ethoxyacetamide hydrochloride as a yellow solid.

Part D

Potassium carbonate (113 g) water (565 mL) were sequentially added to a solution of *N*-{7-bromo-4-[(2-hydroxy-2-methylpropyl)amino][1,5]naphthyridin-3-yl}-2-ethoxyacetamide hydrochloride (113 g, 261 mmol) in denatured ethanol (1.695 L), and the resulting mixture was heated at reflux (77 °C) overnight and allowed to cool to room temperature. The ethanol was removed under reduced pressure, and the resulting mixture was filtered to isolate a solid. The solid was washed with water (100 mL) and dried over two nights in a vacuum oven at 40 °C to provide 90 g of 1-[7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol as a brown solid.

Part E

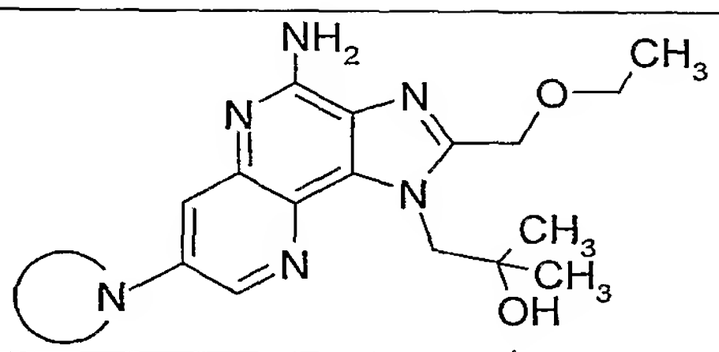
mCPBA (35.5 g of 77% purity, 158 mmol) was added to a stirred solution of 1-[7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (15 g, 0.040 mol) in chloroform (400 mL), and the reaction was stirred at room temperature for 2.5 hours. Concentrated ammonium hydroxide (200 mL) was added, and

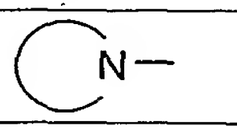
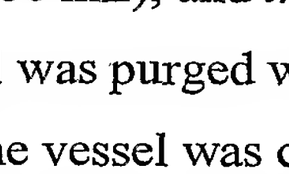
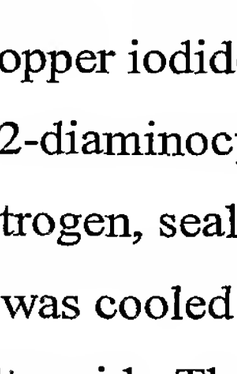
then *p*-toluenesulfonyl chloride (18.9 g, 98.9 mmol) was added over a period of five minutes. The reaction mixture was stirred at room temperature for 2.5 hours, and an analysis by LC/MS indicated the presence of starting material. Additional *p*-toluenesulfonyl chloride (11 g) was added, and the reaction mixture was stirred at room temperature for one hour. An analysis by LC/MS indicated the reaction was still incomplete. Additional ammonium hydroxide (100 mL) and *p*-toluenesulfonyl chloride (10 g) were added, and the mixture was stirred for 30 minutes at room temperature. The aqueous layer was separated and extracted with dichloromethane (2 x 300 mL). The combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue (41.4 g) was purified by chromatography using a Biotage Horizon™ High-Performance Flash Chromatography instrument (65I cartridge, eluting with ethyl acetate:methanol in a gradient from 97:3 to 85:15) to provide 5.96 g of 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol as a yellow solid.

Part F

An amide from the table below (1.2 eq) was added to a test tube containing 8 mg (0.4 eq) of copper iodide, 42 mg of potassium phosphate, and a magnetic stir bar. A solution of 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (38 mg, 1.0 eq) in 1,4-dioxane (1.0 mL) was added to the test tube and the test tube was purged with nitrogen. A solution of *N,N*-dimethylethylenediamine (4.4 µL) in 1,4-dioxane (25 µL) was added to the test tube and the test tube was purged with nitrogen. The test tube was capped and the reaction mixture was stirred at 110 °C for 140 hours.

The reaction mixture was filtered and then concentrated by vacuum centrifugation. The compounds were purified as described in Examples 15 – 30. The table below shows the amide used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



Example	Reagent		Measured Mass (M+H)
31	(S)-(-)-4-Hydroxy-2- pyrrolidinone		415.2107
32	(R)-(-)-5-(Hydroxymethyl)-2-pyrrolidinone		429.2255

Examples 33 – 66

Part A

A reaction vessel was charged sequentially with 1-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol (3.9 g, 10 mmol), S(-)-5-hydroxymethyl-2-pyrrolidinone (1.38 g, 12 mmol), copper iodide (0.76 g, 4 mmol), potassium phosphate (4.25 g, 20 mmol), dioxane (60 mL), and *trans*-1,2-diaminocyclohexane (0.46 g, 4 mmol). The vessel was purged with nitrogen, sealed, and then heated in a sand bath at 100 °C overnight. The vessel was cooled and then S(-)-5-hydroxymethyl-2-pyrrolidinone (1.38 g, 12 mmol), copper iodide (0.76 g, 4 mmol), potassium phosphate (4.25 g, 20 mmol), and *trans*-1,2-diaminocyclohexane (0.46 g, 4 mmol) were added and the vessel was purged with nitrogen, sealed, and then heated in a sand bath at 100 °C overnight. The reaction mixture was cooled to ambient temperature and then it was filtered through a layer of CELITE filter aid. The filter cake was rinsed with chloroform and the filtrate was concentrated under reduced pressure to provide an oil. The oil was purified by high performance flash chromatography using a COMBIFLASH system (an automated high-performance flash purification product available from Teledyne Isco, Inc., Lincoln, Nebraska, USA) eluting with a gradient of 0 to 13% methanol in dichloromethane containing 1% ammonium hydroxide to provide 1.56 g of a yellow solid. This material was again purified by high performance flash chromatography

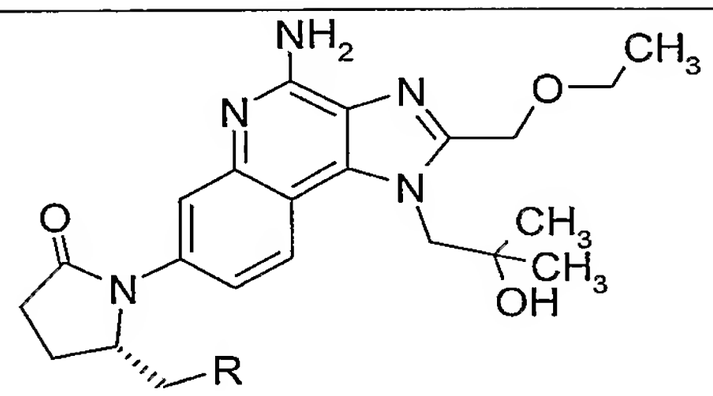
eluting with a gradient of 4 to 14 % CMA in chloroform to provide 1.3 g of 5(S)-1-[4-amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]-5-hydroxymethylpyrrolidin-2-one as a yellow oil.

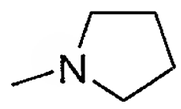
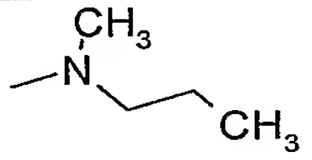
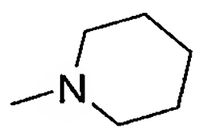
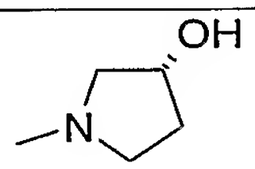
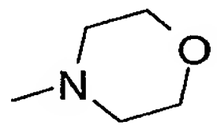
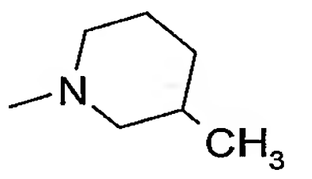
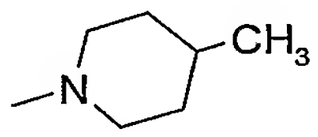
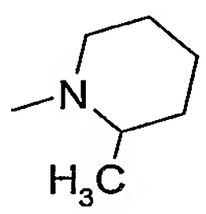
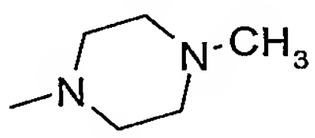
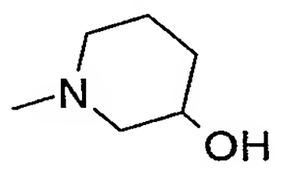
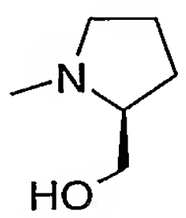
Part B

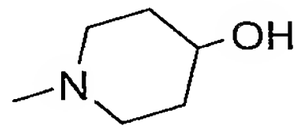
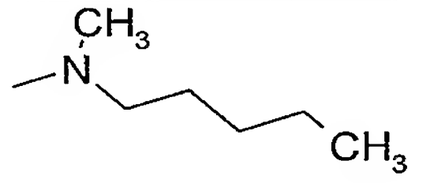
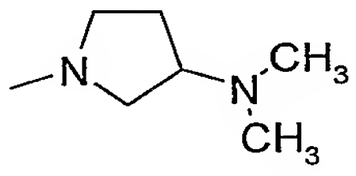
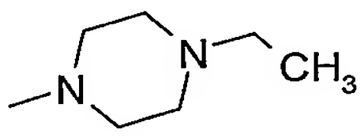
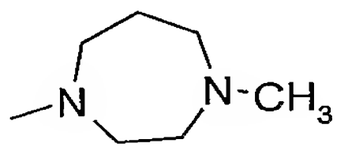
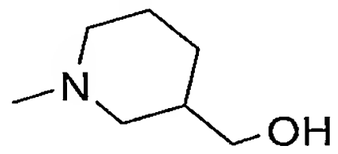
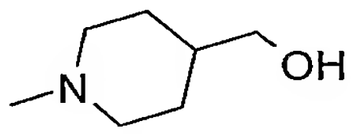
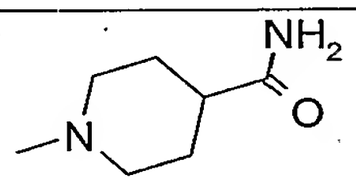
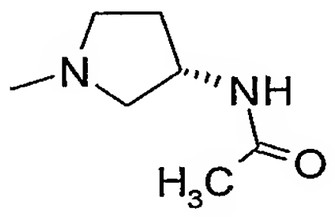
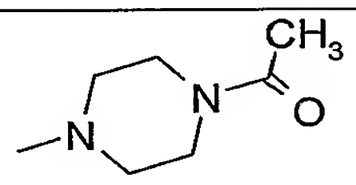
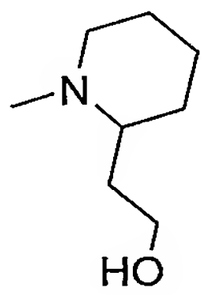
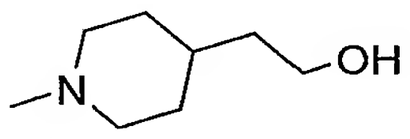
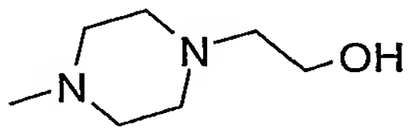
A mixture of the material from Part A (1.26 g, 2.93 mmol), triethylamine (488 µL, 3.51 mmol), and dichloromethane (20 mL) was cooled in an ice bath for 5 minutes. Methanesulfonyl chloride (231 µL) was added dropwise. The reaction mixture was stirred at 0 °C for 2 hours. An additional equivalent of triethylamine and methane sulfonyl chloride were added. The reaction mixture was stirred for 2 hours while slowly warming to ambient temperature. The reaction mixture was quenched with water (about 1 mL) and then concentrated under reduced pressure to provide 3.0 g of crude {(2S)-1-[4-amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]-5-oxopyrrolidin-2-yl}methyl methanesulfonate.

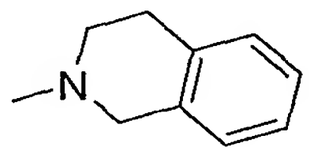
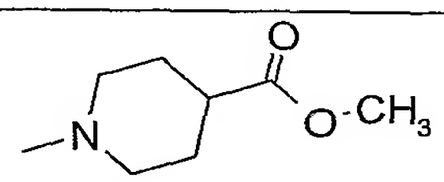
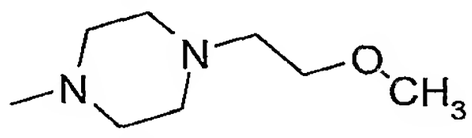
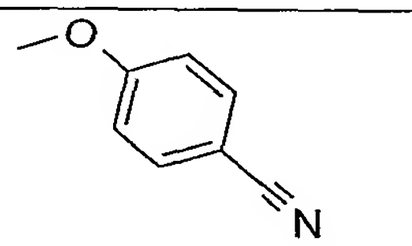
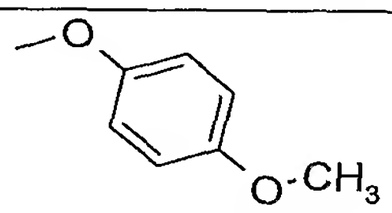
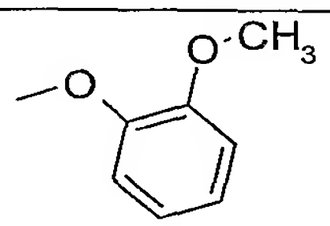
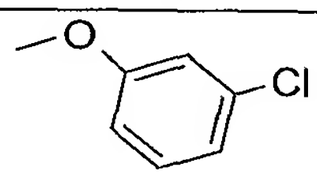
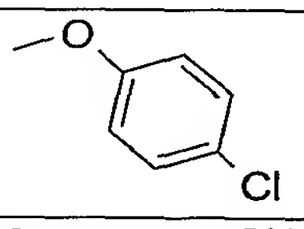
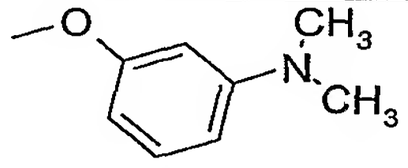
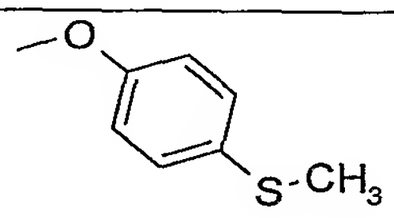
Part C

A reagent from the table below (3.0 eq) was added to a test tube containing a solution of material from Part B (51 mg, 1.0 eq) in *N*,*N*-dimethylacetamide (1.0 mL). Potassium *tert*-butoxide (200 µL of 1 M in tetrahydrofuran) was added. The tubes for Examples 34 - 60 were heated at 70 °C overnight and those for Examples 61 - 67 were heated at 90 °C overnight. The solvent was removed by vacuum centrifugation and the compounds were purified as described in Examples 15 – 30. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



Example	Reagent	R	Measured Mass (M+H)
33	Pyrrolidine		481.2959
34	Methyl-*N*-propylamine		483.3098
35	Piperidine		495.3090
36	(*R*)-3-Hydroxypyrrolidine		497.2879
37	Morpholine		497.2883
38	3-Methylpiperidine		509.3248
39	4-Methylpiperidine		509.3271
40	2-Methylpiperidine		509.3259
41	1-Methylpiperazine		510.3237
42	3-Hydroxypiperidine		511.3053
43	*L*-Prolinol		511.3016

44	4-Hydroxypiperidine		511.3048
45	*N*-Methylpentylamine		511.3370
46	3-(Dimethylamino)pyrrolidine		524.3369
47	*N*-Ethylpiperazine		524.3355
48	*N*-Methylhomopiperazine		524.3365
49	3-(Hydroxymethyl)piperidine		525.3239
50	4-(Hydroxymethyl)piperidine		525.3190
51	Isonipecotamide		538.3169
52	(3*S*)-(-)-3-Acetamidopyrrolidine		538.3168
53	1-Acetylpiperazine		538.3150
54	2-Piperidineethanol		539.3353
55	4-Piperidineethanol		539.3375
56	*N*-(2-Hydroxyethyl)piperazine		540.3286

57	1,2,3,4-Tetrahydroisoquinoline		543.3088
58	Methyl isonipecotate		553.3162
59	1-(2-Methoxyethyl)piperazine		554.3436
60	4-Cyanophenol		529.2554
61	4-Methoxyphenol		534.2681
62	Guaiacol		534.2712
63	3-Chlorophenol		538.2236
64	4-Chlorophenol		538.2228
65	3-Dimethylaminophenol		547.3030
66	4-(Methylmercapto)phenol		550.2490

Examples 67 and 68

Part A

1-[4-Amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol (3.9 g, 10 mmol) was reacted with R(-)-5-hydroxymethyl-2-pyrrolidinone (1.38 g, 12 mmol) according to the method of Part A of Examples 34 – 67. The crude product was purified by high performance flash chromatography using a

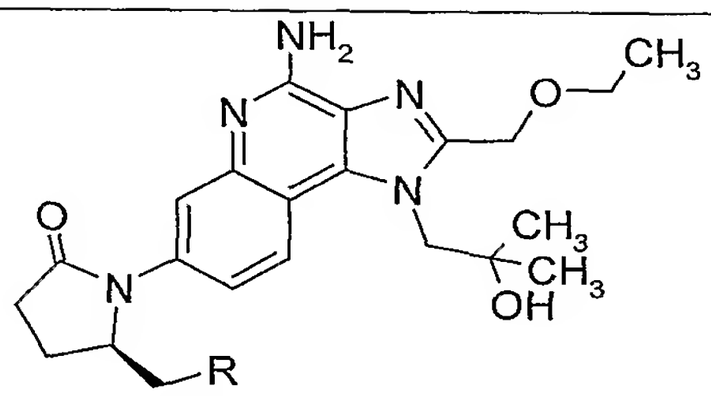
COMBIFLASH system eluting with a gradient of 0 to 13% methanol in dichloromethane containing 1% ammonium hydroxide to provide 1.28 g of (5R)-1-[4-amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]-5-hydroxymethylpyrrolidin-2-one as a yellow solid.

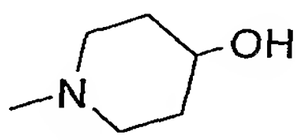
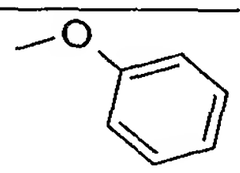
Part B

A mixture of the material from Part A (1.26 g, 2.95 mmol), triethylamine (493 µL, 3.54 mmol), and dichloromethane (20 mL) was cooled in an ice bath for 5 minutes. Methanesulfonyl chloride (233 µL, 2.95 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 2 hours. Additional methanesulfonyl chloride (30 µL) was added and the reaction mixture was stirred at 0 °C for an additional 30 minutes. The reaction mixture was concentrated under reduced pressure. The residue was diluted with diethyl ether and the mixture was concentrated under reduced pressure to provide 2.2 g of crude {(2R)-1-[4-amino-2-ethoxymethyl-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]-5-oxopyrrolidin-2-yl}methyl methanesulfonate.

Part C

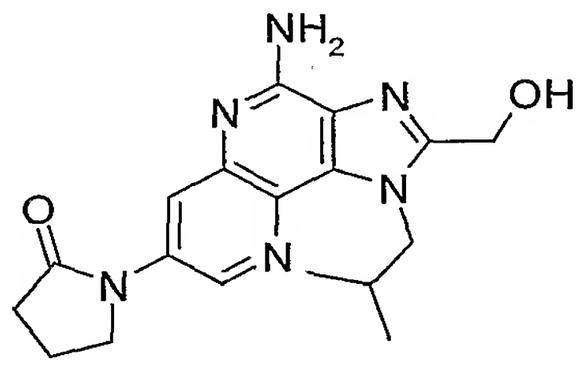
A reagent from the table below (3.0 eq) was added to a test tube containing a solution of material from Part B (55 mg, 1.0 eq) in *N,N*-dimethylacetamide (1.0 mL) and potassium *tert*-butoxide (200 µL of 1 M in tetrahydrofuran). The tube for Example 68 was heated at 50 °C for 6 hours and the tube for Example 69 was heated at 70 °C for 6 hours overnight. The solvent was removed by vacuum centrifugation and the compounds were purified as described in Examples 15 – 30. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



Example	Reagent	R	Measured Mass (M+H)
67	4-Hydroxypiperidine		511.3026
68	Phenol		504.2630

Example 69

1-[4-Amino-2-(hydroxymethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-c][1,5]naphthyridin-7-yl]pyrrolidin-2-one



1-[4-Amino-2-(ethoxymethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]-1,5-naphthyridin-7-yl]pyrrolidin-2-one (0.150 g, 0.39 mmol) from Example 13 was dissolved in dichloromethane (5 mL) and cooled with an ice bath. Boron tribromide (0.5 mL of a 1.0 M solution in dichloromethane) was added dropwise over 1 minute. The resulting slurry was stirred for 16 hours. The reaction mixture was acidified with 6 N hydrochloric acid (3 mL). The mixture was stirred until all of the solids dissolved. The biphasic mixture was made basic with 50% aqueous sodium hydroxide (~6 mL). The layers were separated and the aqueous fraction was extracted with dichloromethane, followed by extraction with a 10% methanol in dichloromethane solution. The organic fractions were combined and concentrated under vacuum. The residue was purified by HPFC eluting with a linear gradient of 2-30 % CMA in chloroform. Recrystallization from acetonitrile

afforded 1-[4-amino-2-(hydroxymethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-7-yl]pyrrolidin-2-one as 0.034 g of a white powder, m.p. 233-235 °C.

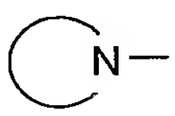
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.93 (d, J = 2.4 Hz, 1H), 8.10 (d, J = 2.4 Hz, 1H), 6.84 (s, 2H), 5.66 (t, J = 5.7 Hz, 1H), 4.77 (d, J = 5.7 Hz, 2H), 4.69 (d, J = 7.5 Hz, 2H), 3.98 (t, J = 7.0 Hz, 2H), 2.55 (t, J = 8.0 Hz, 2H), 2.46-2.34 (m, 1H), 2.13 (quintet, J = 7.5 Hz, 2H), 0.90 (d, J = 6.7 Hz, 6H).

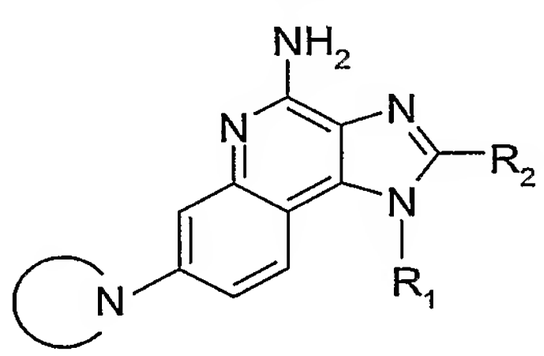
^{13}C NMR (125 MHz, DMSO-d_6) δ 174.3, 152.7, 152.6, 140.3, 135.6, 134.6, 132.7, 129.9, 127.9, 121.2, 56.2, 51.8, 47.7, 32.0, 29.1, 19.4, 17.6.

MS(ESI) m/z 355.1898 (355.1882 calcd. for $C_{18}H_{22}N_6O_2$, M+H);

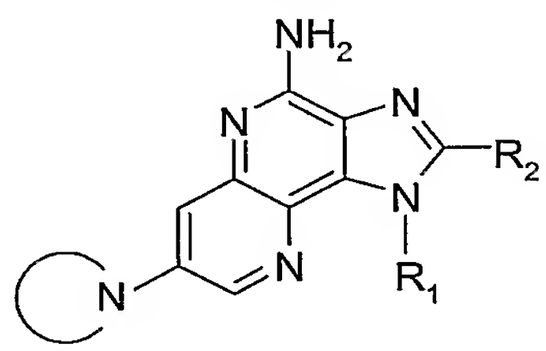
Anal. Calcd. for $C_{23}H_{31}N_5O_3$•2.25H_2O: %C, 54.74; %H, 6.76; %N, 21.28. Found: %C, 54.68; %H, 6.60; %N, 20.91.

Exemplary Compounds

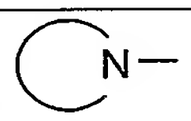
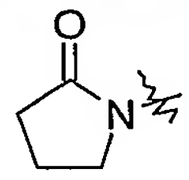
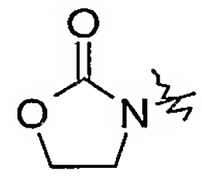
Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (IIb and IIIa) wherein R_1, R_2, and  are defined immediately below in the table. In this table, for each ring system (Formula IIb or Formula IIIa), each row represents one specific compound.

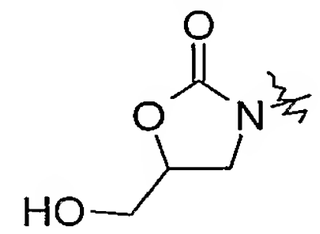
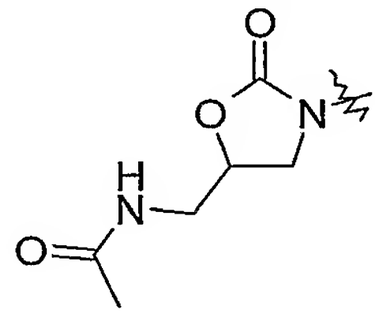
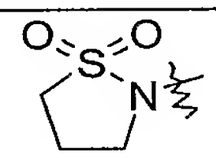
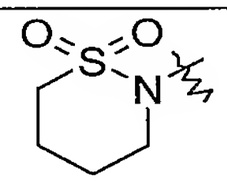
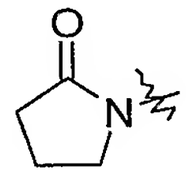
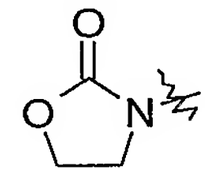
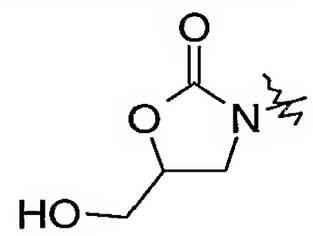
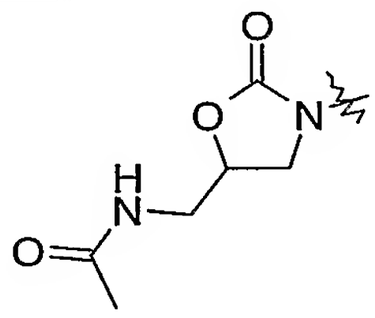
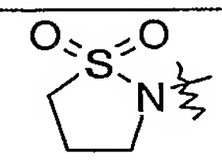
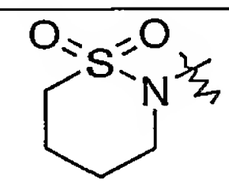


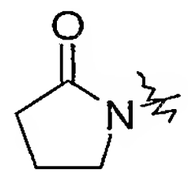
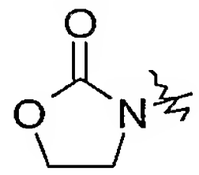
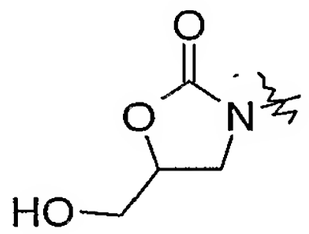
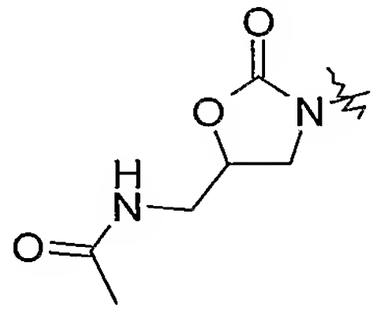
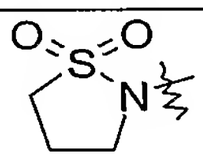
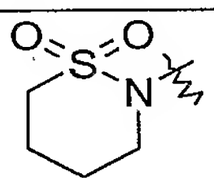
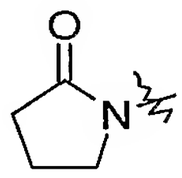
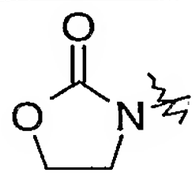
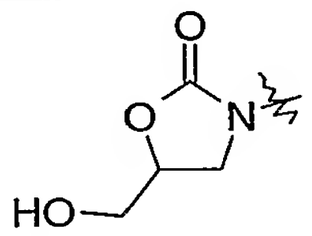
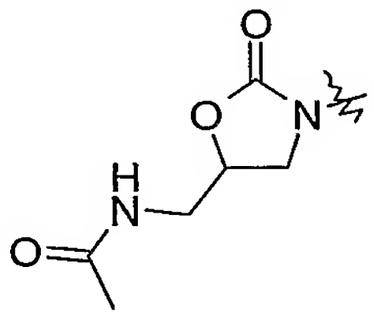
IIb

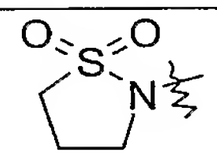
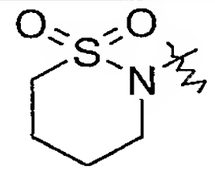
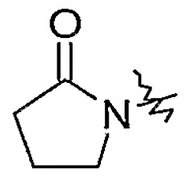
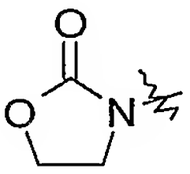
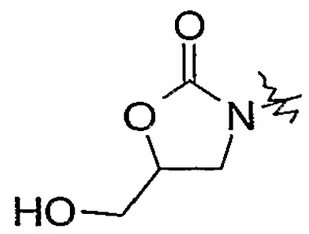
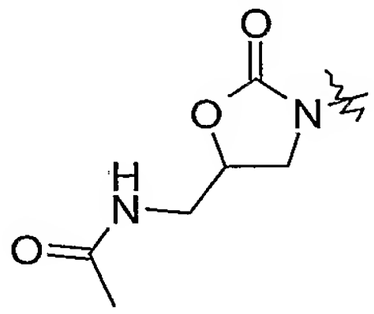
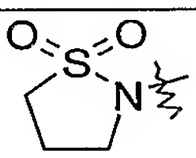
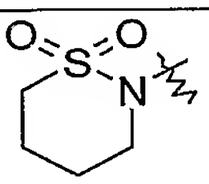
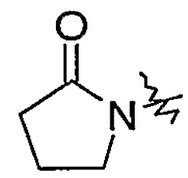
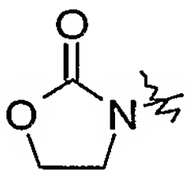


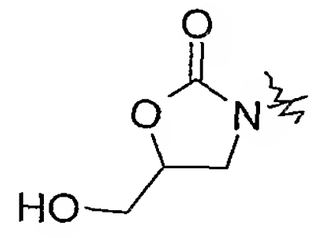
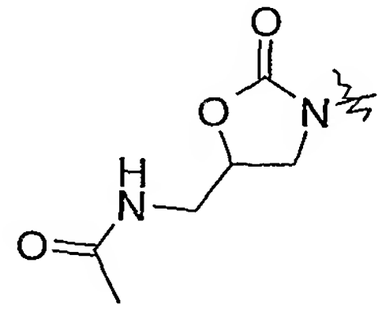
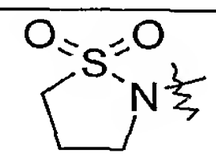
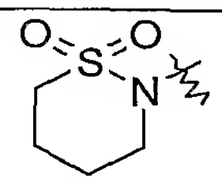
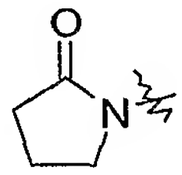
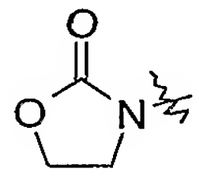
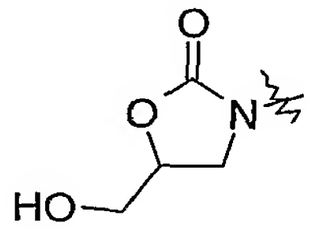
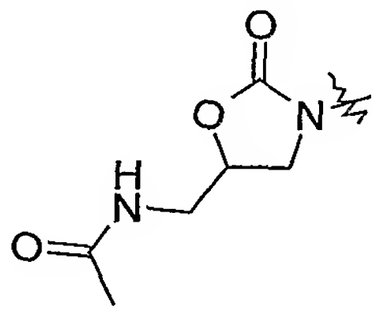
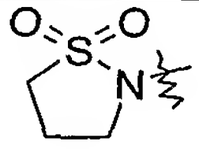
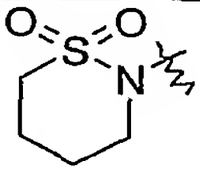
IIIa

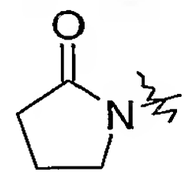
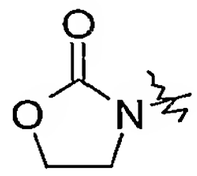
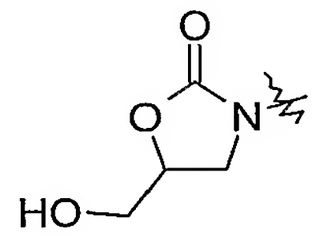
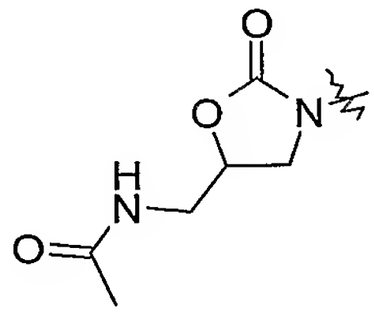
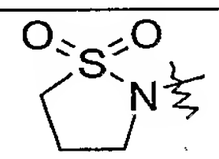
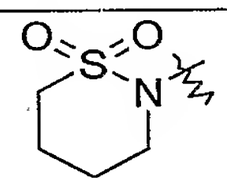
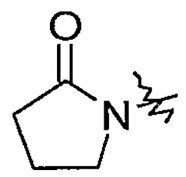
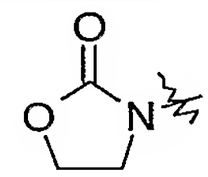
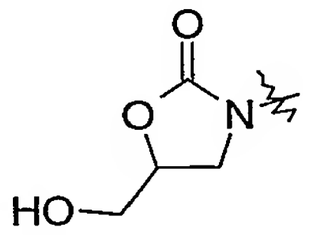
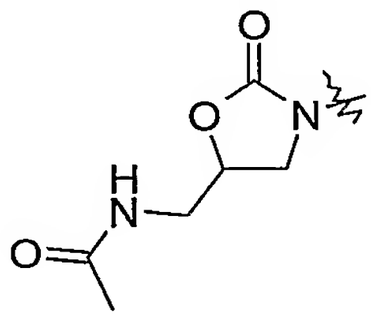
R_1	R_2	
2-hydroxy-2-methylpropyl	ethyl	
2-hydroxy-2-methylpropyl	ethyl	

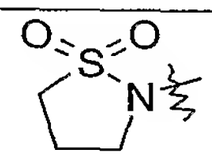
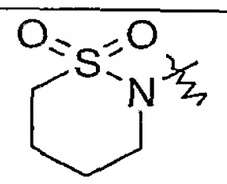
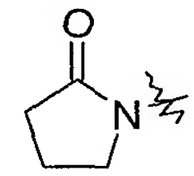
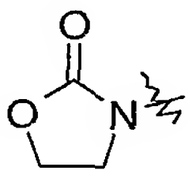
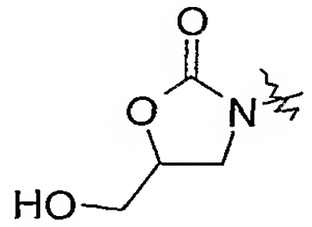
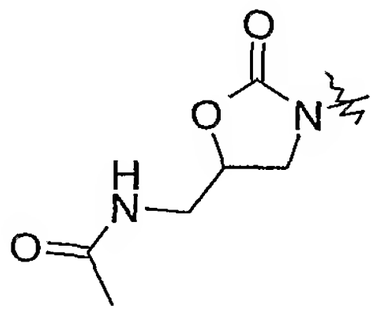
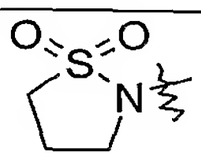
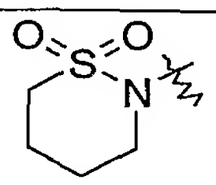
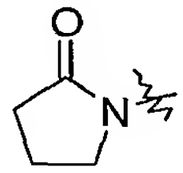
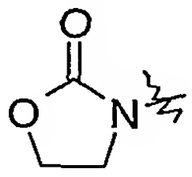
2-hydroxy-2-methylpropyl	ethyl	
2-hydroxy-2-methylpropyl	ethyl	
2-hydroxy-2-methylpropyl	ethyl	
2-hydroxy-2-methylpropyl	ethyl	
2-hydroxy-2-methylpropyl	*n*-propyl	
2-hydroxy-2-methylpropyl	*n*-propyl	
2-hydroxy-2-methylpropyl	*n*-propyl	
2-hydroxy-2-methylpropyl	*n*-propyl	
2-hydroxy-2-methylpropyl	*n*-propyl	
2-hydroxy-2-methylpropyl	*n*-propyl	

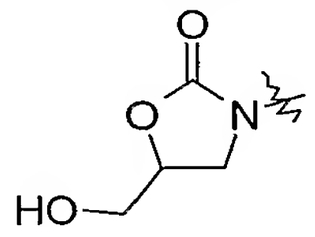
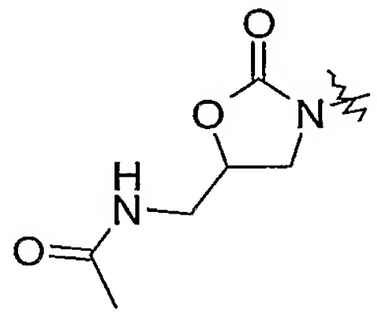
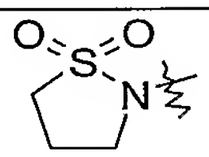
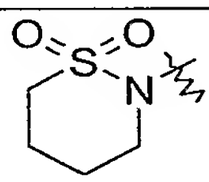
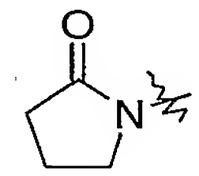
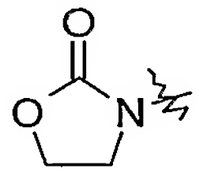
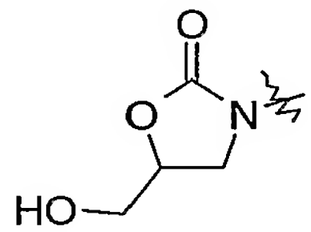
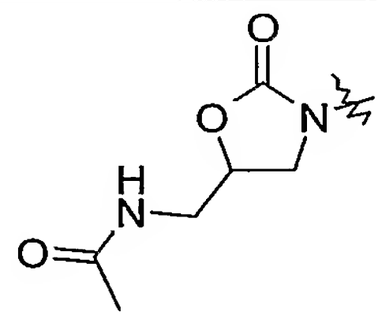
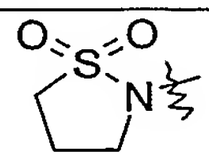
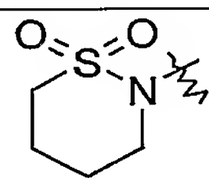
2-hydroxy-2-methylpropyl	methoxymethyl	
2-hydroxy-2-methylpropyl	methoxymethyl	
2-hydroxy-2-methylpropyl	methoxymethyl	
2-hydroxy-2-methylpropyl	methoxymethyl	
2-hydroxy-2-methylpropyl	methoxymethyl	
2-hydroxy-2-methylpropyl	methoxymethyl	
2-hydroxy-2-methylpropyl	ethoxymethyl	
2-hydroxy-2-methylpropyl	ethoxymethyl	
2-hydroxy-2-methylpropyl	ethoxymethyl	
2-hydroxy-2-methylpropyl	ethoxymethyl	

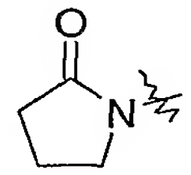
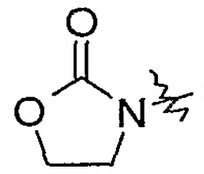
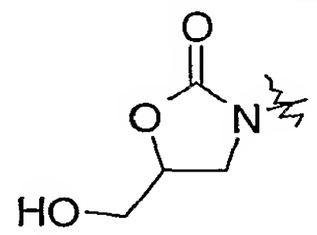
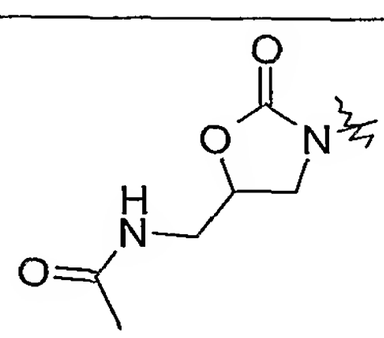
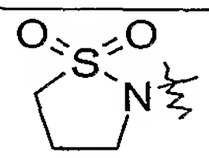
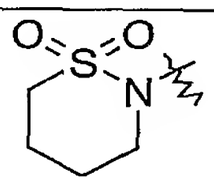
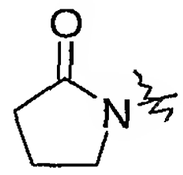
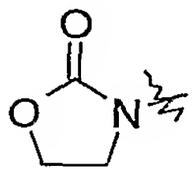
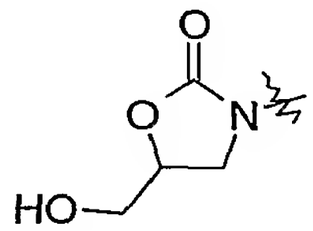
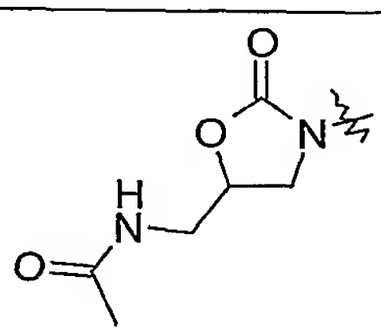
2-hydroxy-2-methylpropyl	ethoxymethyl	
2-hydroxy-2-methylpropyl	ethoxymethyl	
2-hydroxy-2-methylpropyl	2-methoxyethyl	
2-hydroxy-2-methylpropyl	2-methoxyethyl	
2-hydroxy-2-methylpropyl	2-methoxyethyl	
2-hydroxy-2-methylpropyl	2-methoxyethyl	
2-hydroxy-2-methylpropyl	2-methoxyethyl	
2-hydroxy-2-methylpropyl	2-methoxyethyl	
2-hydroxy-2-methylpropyl	hydroxymethyl	
2-hydroxy-2-methylpropyl	hydroxymethyl	

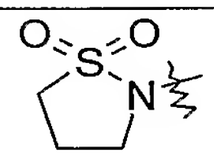
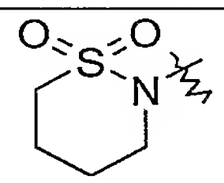
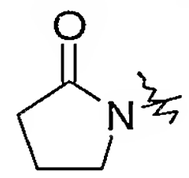
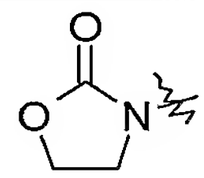
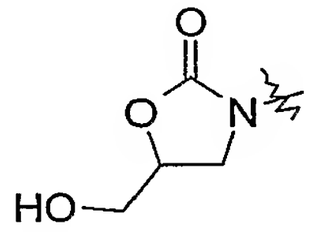
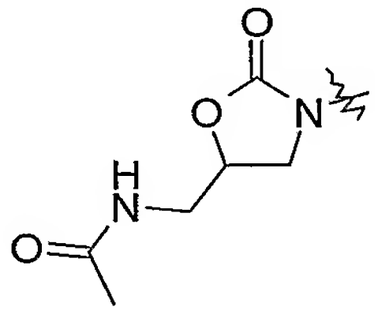
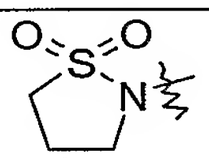
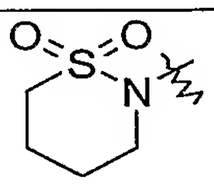
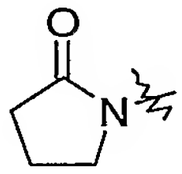
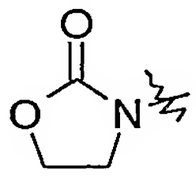
2-hydroxy-2-methylpropyl	hydroxymethyl	
2-hydroxy-2-methylpropyl	hydroxymethyl	
2-hydroxy-2-methylpropyl	hydroxymethyl	
2-hydroxy-2-methylpropyl	hydroxymethyl	
2-hydroxy-2-methylpropyl	2-hydroxyethyl	
2-hydroxy-2-methylpropyl	2-hydroxyethyl	
2-hydroxy-2-methylpropyl	2-hydroxyethyl	
2-hydroxy-2-methylpropyl	2-hydroxyethyl	
2-hydroxy-2-methylpropyl	2-hydroxyethyl	
2-hydroxy-2-methylpropyl	2-hydroxyethyl	

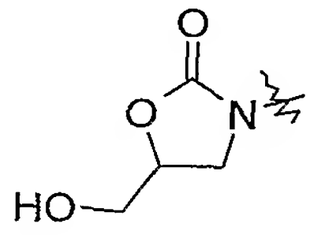
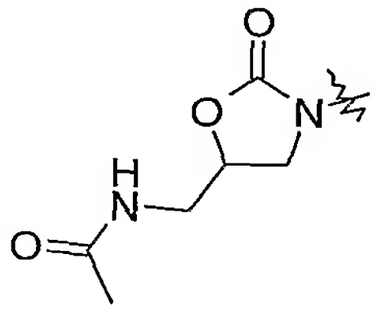
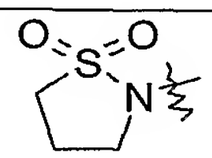
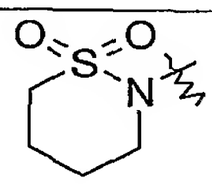
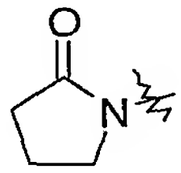
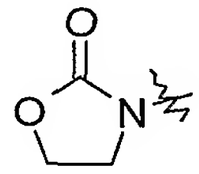
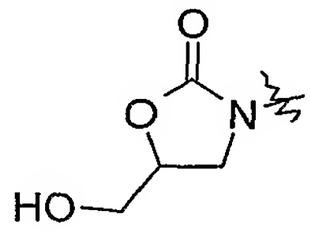
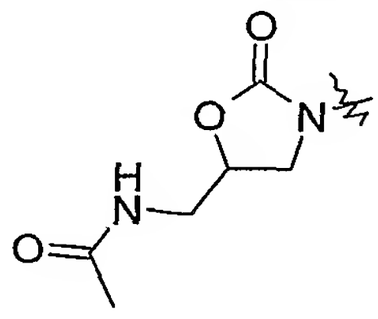
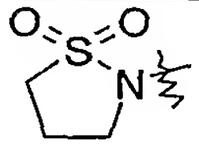
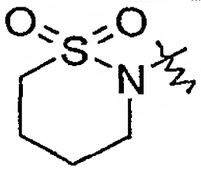
2-methylpropyl	ethyl	
2-methylpropyl	ethyl	
2-methylpropyl	ethyl	
2-methylpropyl	ethyl	
2-methylpropyl	ethyl	
2-methylpropyl	ethyl	
2-methylpropyl	*n*-propyl	
2-methylpropyl	*n*-propyl	
2-methylpropyl	*n*-propyl	
2-methylpropyl	*n*-propyl	

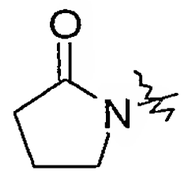
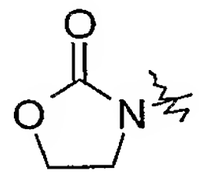
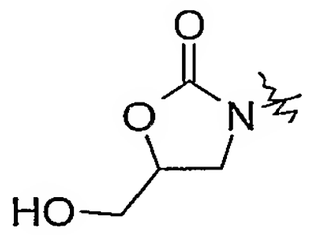
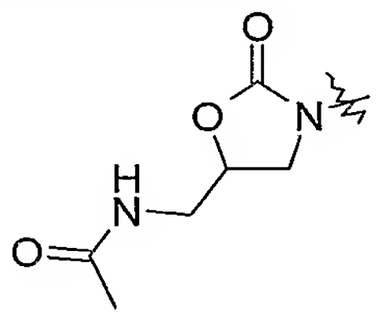
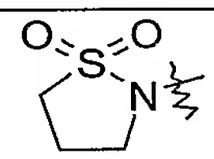
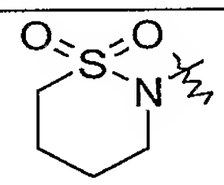
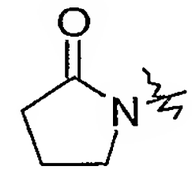
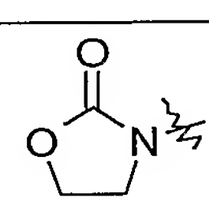
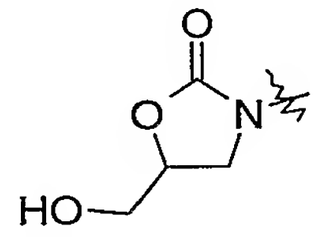
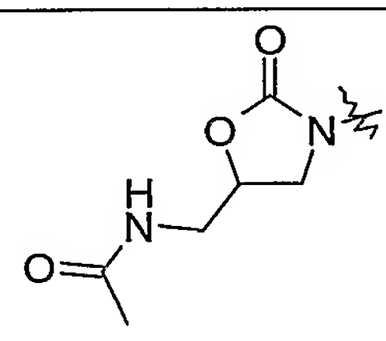
2-methylpropyl	*n*-propyl	
2-methylpropyl	*n*-propyl	
2-methylpropyl	methoxymethyl	
2-methylpropyl	methoxymethyl	
2-methylpropyl	methoxymethyl	
2-methylpropyl	methoxymethyl	
2-methylpropyl	methoxymethyl	
2-methylpropyl	methoxymethyl	
2-methylpropyl	ethoxymethyl	
2-methylpropyl	ethoxymethyl	

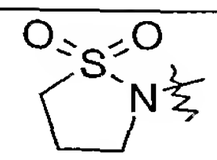
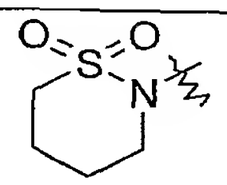
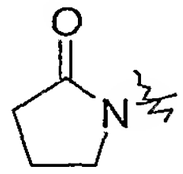
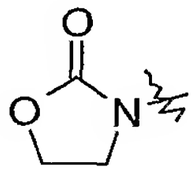
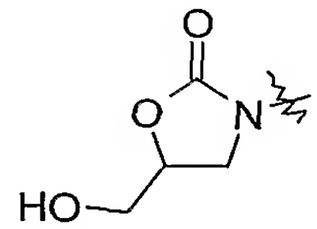
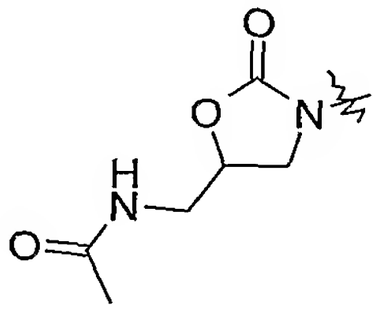
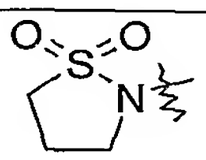
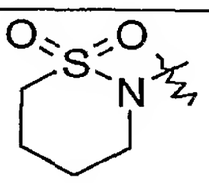
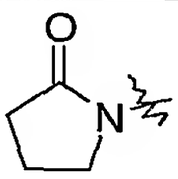
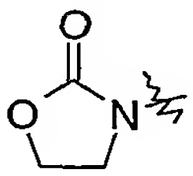
2-methylpropyl	ethoxymethyl	
2-methylpropyl	ethoxymethyl	
2-methylpropyl	ethoxymethyl	
2-methylpropyl	ethoxymethyl	
2-methylpropyl	2-methoxyethyl	
2-methylpropyl	2-methoxyethyl	
2-methylpropyl	2-methoxyethyl	
2-methylpropyl	2-methoxyethyl	
2-methylpropyl	2-methoxyethyl	
2-methylpropyl	2-methoxyethyl	

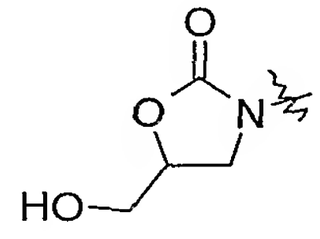
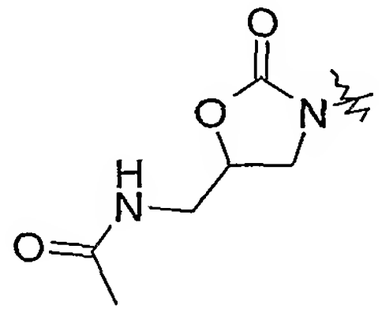
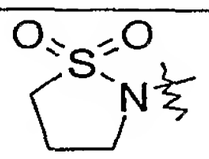
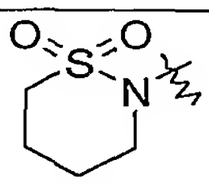
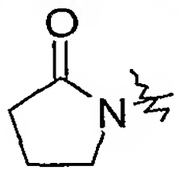
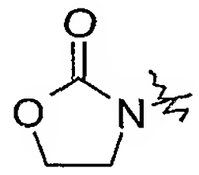
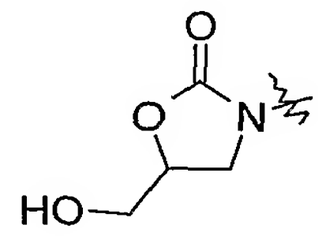
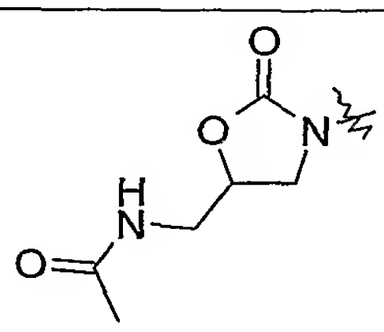
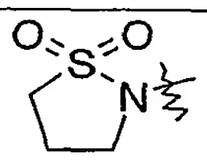
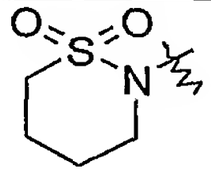
2-methylpropyl	hydroxymethyl	
2-methylpropyl	hydroxymethyl	
2-methylpropyl	hydroxymethyl	
2-methylpropyl	hydroxymethyl	
2-methylpropyl	hydroxymethyl	
2-methylpropyl	hydroxymethyl	
2-methylpropyl	2-hydroxyethyl	
2-methylpropyl	2-hydroxyethyl	
2-methylpropyl	2-hydroxyethyl	
2-methylpropyl	2-hydroxyethyl	

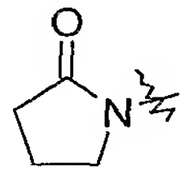
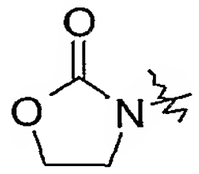
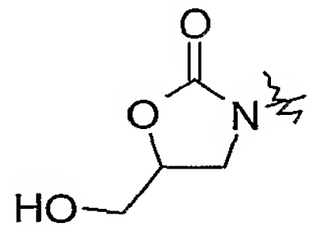
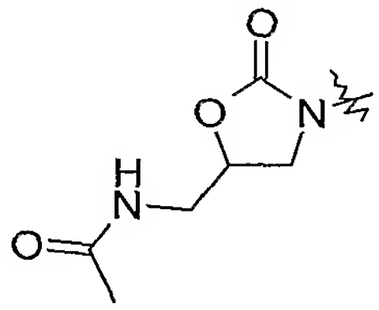
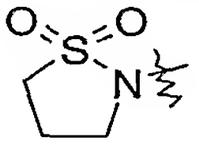
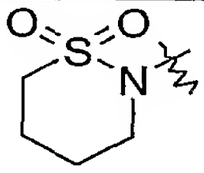
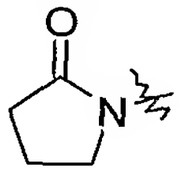
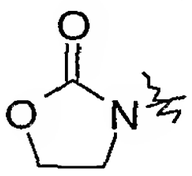
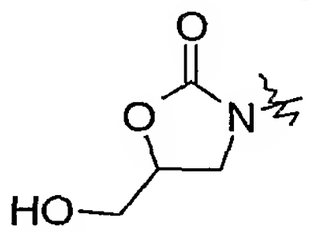
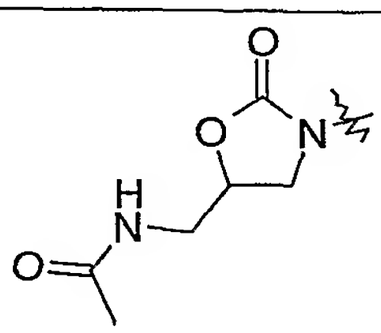
2-methylpropyl	2-hydroxyethyl	
2-methylpropyl	2-hydroxyethyl	
n-propyl	ethyl	
n-propyl	ethyl	
n-propyl	ethyl	
n-propyl	ethyl	
n-propyl	ethyl	
n-propyl	ethyl	
n-propyl	*n*-propyl	
n-propyl	*n*-propyl	

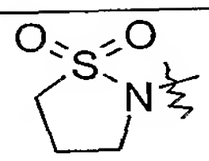
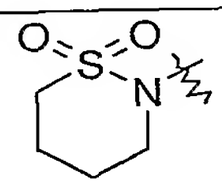
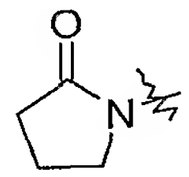
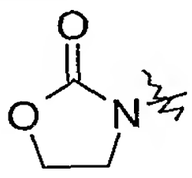
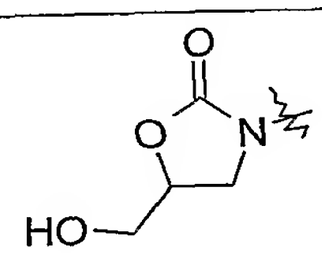
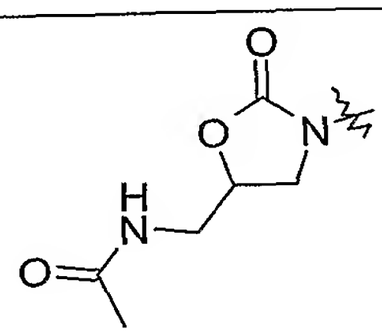
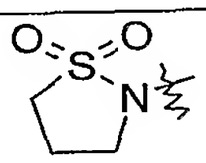
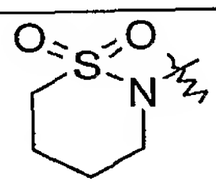
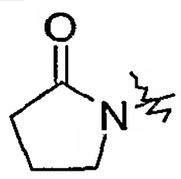
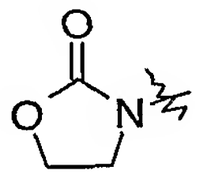
n-propyl	*n*-propyl	
n-propyl	*n*-propyl	
n-propyl	*n*-propyl	
n-propyl	*n*-propyl	
n-propyl	methoxymethyl	
n-propyl	methoxymethyl	
n-propyl	methoxymethyl	
n-propyl	methoxymethyl	
n-propyl	methoxymethyl	
n-propyl	methoxymethyl	

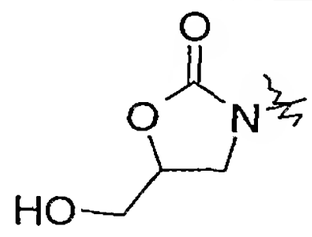
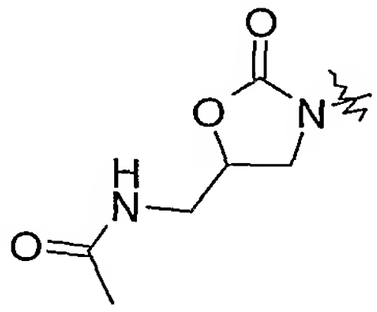
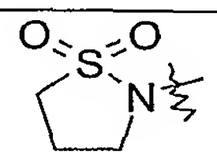
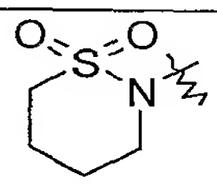
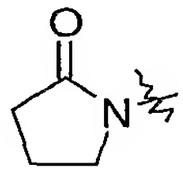
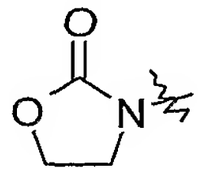
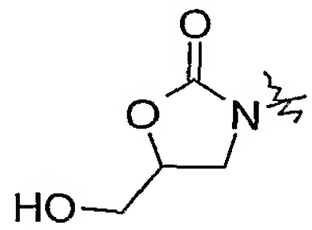
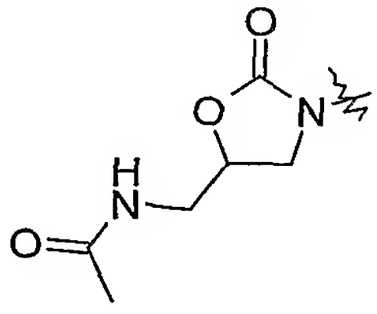
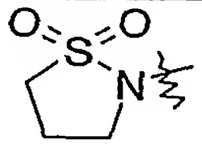
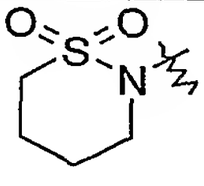
n-propyl	ethoxymethyl	
n-propyl	ethoxymethyl	
n-propyl	ethoxymethyl	
n-propyl	ethoxymethyl	
n-propyl	ethoxymethyl	
n-propyl	ethoxymethyl	
n-propyl	2-methoxyethyl	
n-propyl	2-methoxyethyl	
n-propyl	2-methoxyethyl	
n-propyl	2-methoxyethyl	

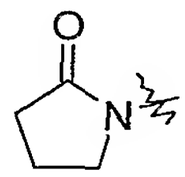
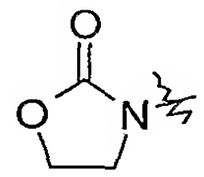
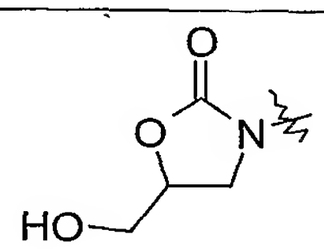
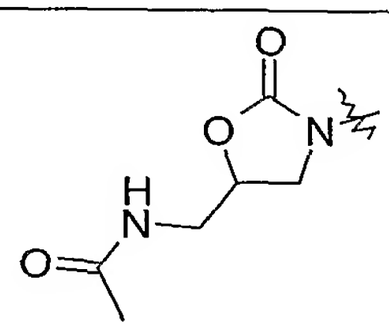
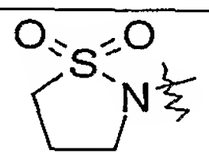
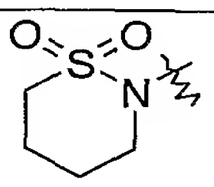
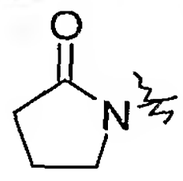
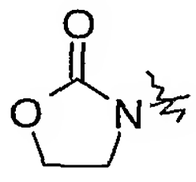
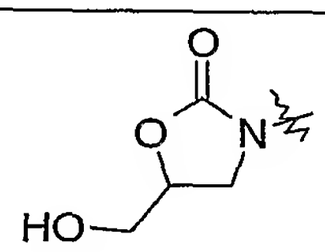
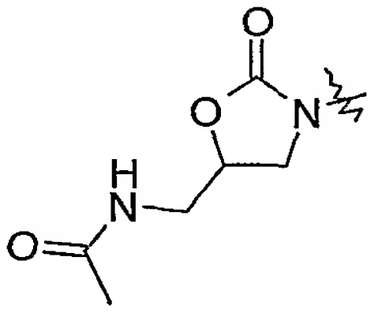
n-propyl	2-methoxyethyl	
n-propyl	2-methoxyethyl	
n-propyl	hydroxymethyl	
n-propyl	hydroxymethyl	
n-propyl	hydroxymethyl	
n-propyl	hydroxymethyl	
n-propyl	hydroxymethyl	
n-propyl	hydroxymethyl	
n-propyl	2-hydroxyethyl	
n-propyl	2-hydroxyethyl	

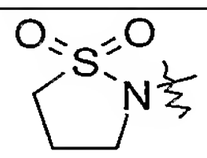
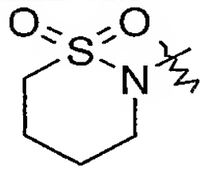
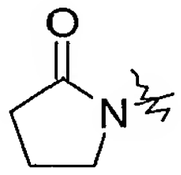
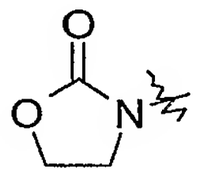
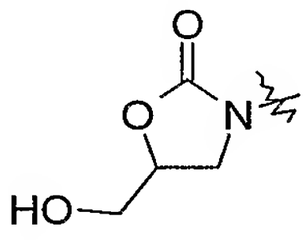
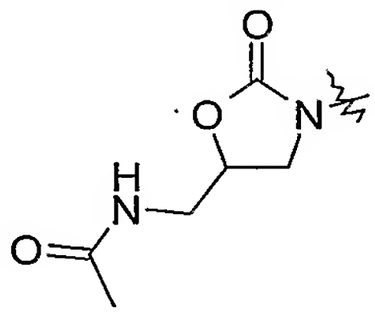
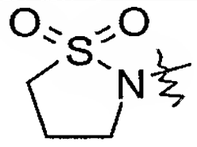
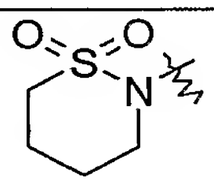
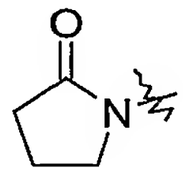
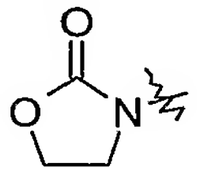
n-propyl	2-hydroxyethyl	
n-propyl	2-hydroxyethyl	
n-propyl	2-hydroxyethyl	
n-propyl	2-hydroxyethyl	
2,3-dihydroxypropyl	ethyl	
2,3-dihydroxypropyl	ethyl	
2,3-dihydroxypropyl	ethyl	
2,3-dihydroxypropyl	ethyl	
2,3-dihydroxypropyl	ethyl	
2,3-dihydroxypropyl	ethyl	

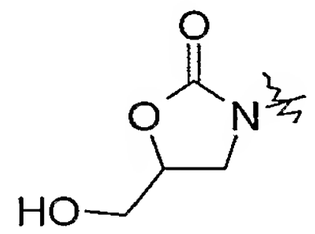
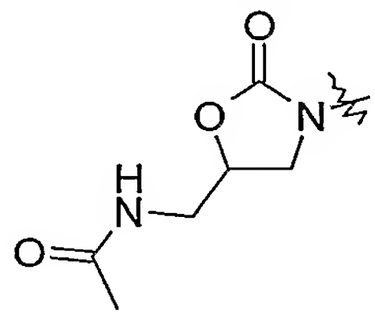
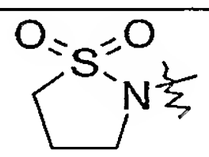
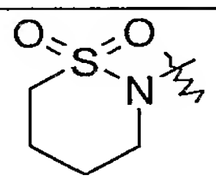
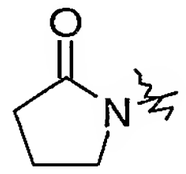
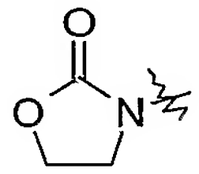
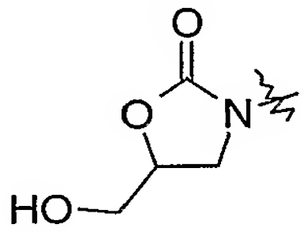
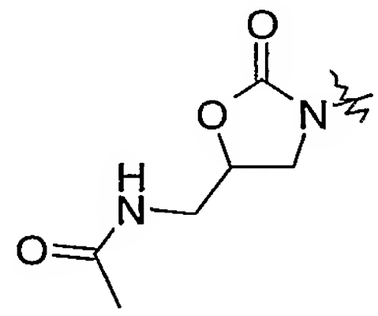
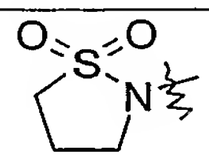
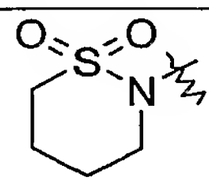
2,3-dihydroxypropyl	*n*-propyl	
2,3-dihydroxypropyl	*n*-propyl	
2,3-dihydroxypropyl	*n*-propyl	
2,3-dihydroxypropyl	*n*-propyl	
2,3-dihydroxypropyl	*n*-propyl	
2,3-dihydroxypropyl	*n*-propyl	
2,3-dihydroxypropyl	methoxymethyl	
2,3-dihydroxypropyl	methoxymethyl	
2,3-dihydroxypropyl	methoxymethyl	
2,3-dihydroxypropyl	methoxymethyl	

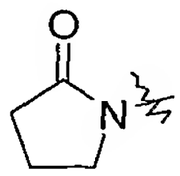
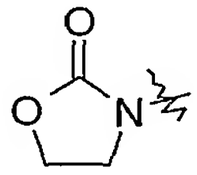
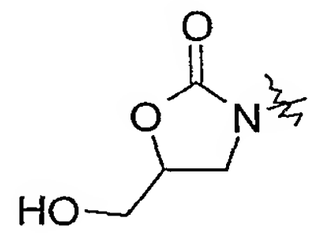
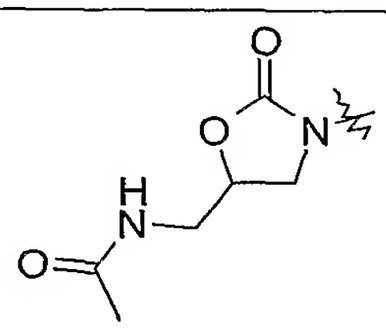
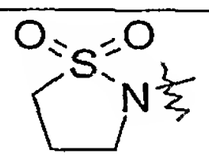
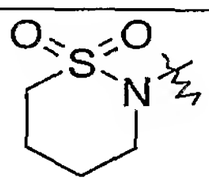
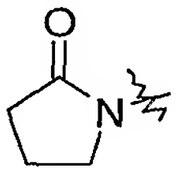
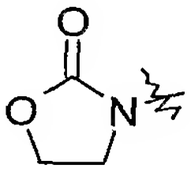
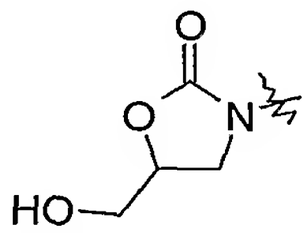
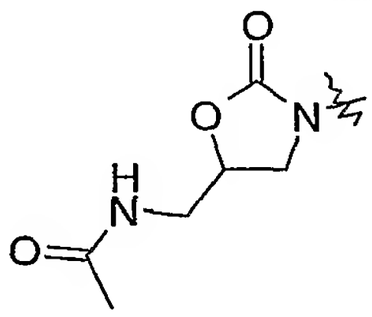
2,3-dihydroxypropyl	methoxymethyl	
2,3-dihydroxypropyl	methoxymethyl	
2,3-dihydroxypropyl	ethoxymethyl	
2,3-dihydroxypropyl	ethoxymethyl	
2,3-dihydroxypropyl	ethoxymethyl	
2,3-dihydroxypropyl	ethoxymethyl	
2,3-dihydroxypropyl	ethoxymethyl	
2,3-dihydroxypropyl	ethoxymethyl	
2,3-dihydroxypropyl	2-methoxyethyl	
2,3-dihydroxypropyl	2-methoxyethyl	

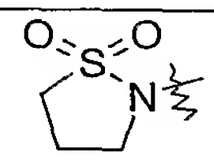
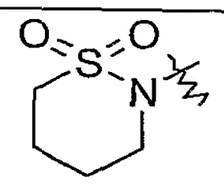
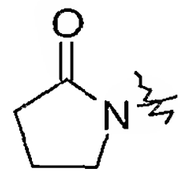
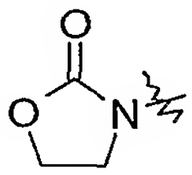
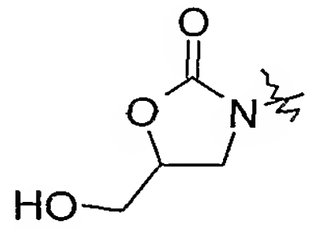
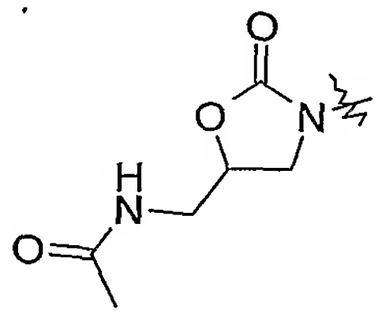
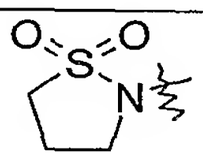
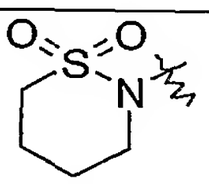
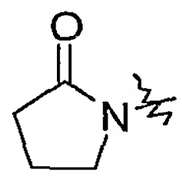
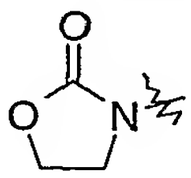
2,3-dihydroxypropyl	2-methoxyethyl	
2,3-dihydroxypropyl	2-methoxyethyl	
2,3-dihydroxypropyl	2-methoxyethyl	
2,3-dihydroxypropyl	2-methoxyethyl	
2,3-dihydroxypropyl	hydroxymethyl	
2,3-dihydroxypropyl	hydroxymethyl	
2,3-dihydroxypropyl	hydroxymethyl	
2,3-dihydroxypropyl	hydroxymethyl	
2,3-dihydroxypropyl	hydroxymethyl	
2,3-dihydroxypropyl	hydroxymethyl	

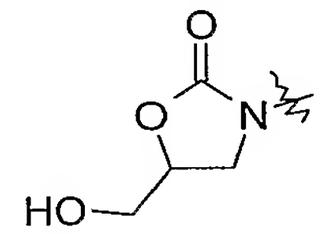
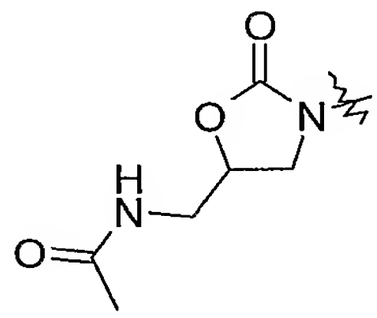
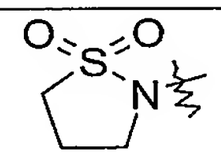
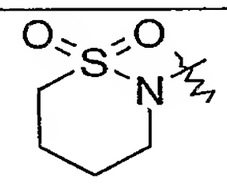
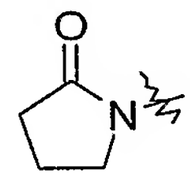
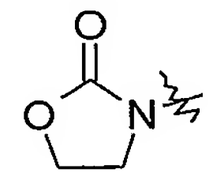
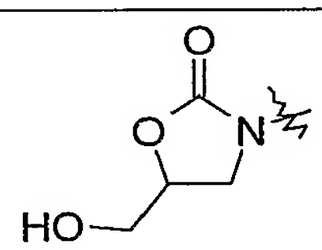
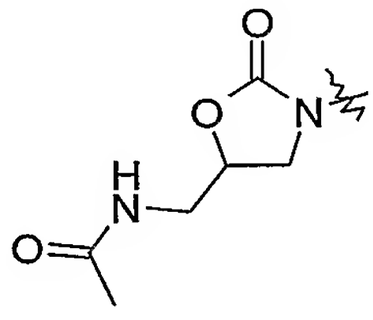
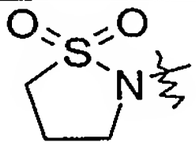
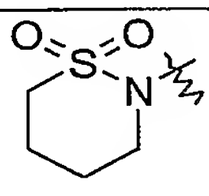
2,3-dihydroxypropyl	2-hydroxyethyl	
2,3-dihydroxypropyl	2-hydroxyethyl	
2,3-dihydroxypropyl	2-hydroxyethyl	
2,3-dihydroxypropyl	2-hydroxyethyl	
2,3-dihydroxypropyl	2-hydroxyethyl	
2,3-dihydroxypropyl	2-hydroxyethyl	
3-(isopropoxy)propyl	ethyl	
3-(isopropoxy)propyl	ethyl	
3-(isopropoxy)propyl	ethyl	
3-(isopropoxy)propyl	ethyl	

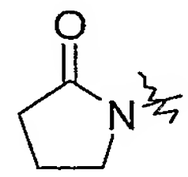
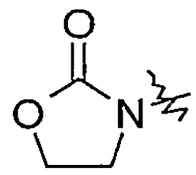
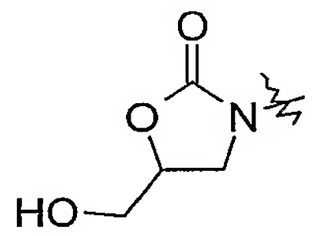
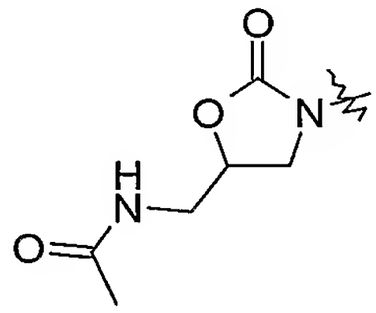
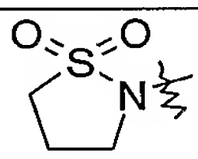
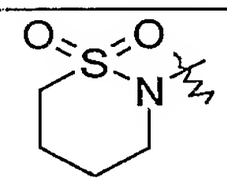
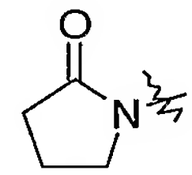
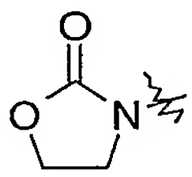
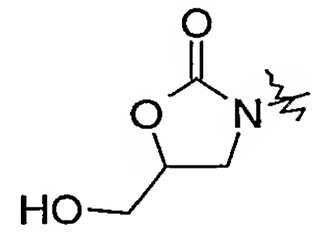
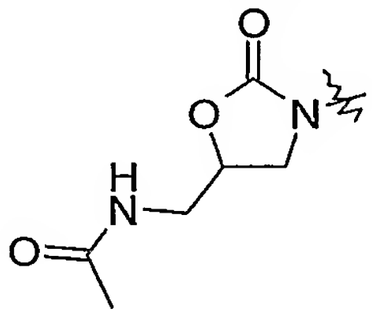
3-(isopropoxy)propyl	ethyl	
3-(isopropoxy)propyl	ethyl	
3-(isopropoxy)propyl	*n*-propyl	
3-(isopropoxy)propyl	*n*-propyl	
3-(isopropoxy)propyl	*n*-propyl	
3-(isopropoxy)propyl	*n*-propyl	
3-(isopropoxy)propyl	*n*-propyl	
3-(isopropoxy)propyl	*n*-propyl	
3-(isopropoxy)propyl	methoxymethyl	
3-(isopropoxy)propyl	methoxymethyl	

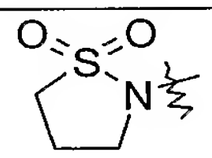
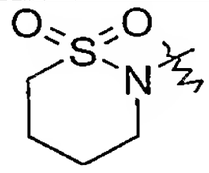
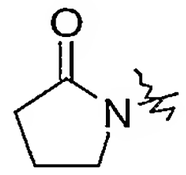
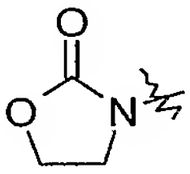
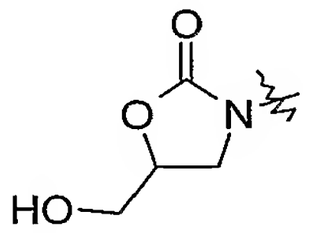
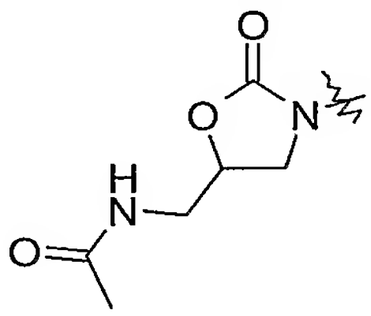
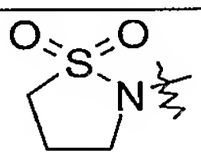
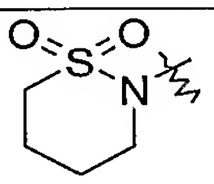
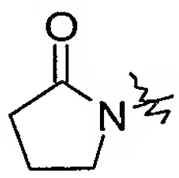
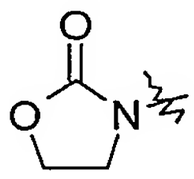
3-(isopropoxy)propyl	methoxymethyl	
3-(isopropoxy)propyl	methoxymethyl	
3-(isopropoxy)propyl	methoxymethyl	
3-(isopropoxy)propyl	methoxymethyl	
3-(isopropoxy)propyl	ethoxymethyl	
3-(isopropoxy)propyl	ethoxymethyl	
3-(isopropoxy)propyl	ethoxymethyl	
3-(isopropoxy)propyl	ethoxymethyl	
3-(isopropoxy)propyl	ethoxymethyl	
3-(isopropoxy)propyl	ethoxymethyl	

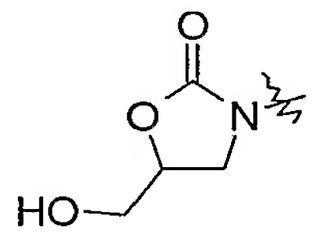
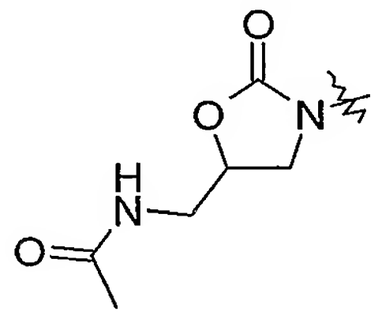
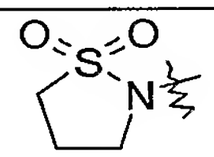
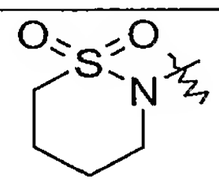
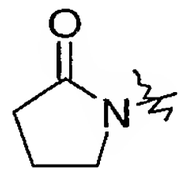
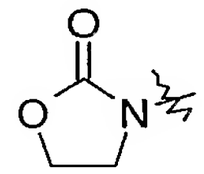
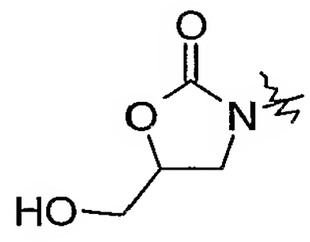
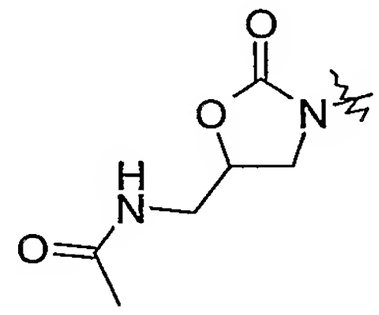
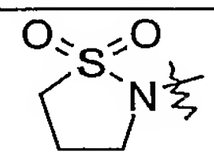
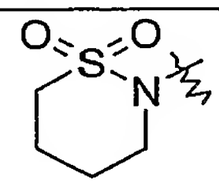
3-(isopropoxy)propyl	2-methoxyethyl	
3-(isopropoxy)propyl	2-methoxyethyl	
3-(isopropoxy)propyl	2-methoxyethyl	
3-(isopropoxy)propyl	2-methoxyethyl	
3-(isopropoxy)propyl	2-methoxyethyl	
3-(isopropoxy)propyl	2-methoxyethyl	
3-(isopropoxy)propyl	hydroxymethyl	
3-(isopropoxy)propyl	hydroxymethyl	
3-(isopropoxy)propyl	hydroxymethyl	
3-(isopropoxy)propyl	hydroxymethyl	

3-(isopropoxy)propyl	hydroxymethyl	
3-(isopropoxy)propyl	hydroxymethyl	
3-(isopropoxy)propyl	2-hydroxyethyl	
3-(isopropoxy)propyl	2-hydroxyethyl	
3-(isopropoxy)propyl	2-hydroxyethyl	
3-(isopropoxy)propyl	2-hydroxyethyl	
3-(isopropoxy)propyl	2-hydroxyethyl	
3-(isopropoxy)propyl	2-hydroxyethyl	
tetrahydropyran-4-ylmethyl	ethyl	
tetrahydropyran-4-ylmethyl	ethyl	

tetrahydropyran-4-ylmethyl	ethyl	
tetrahydropyran-4-ylmethyl	ethyl	
tetrahydropyran-4-ylmethyl	ethyl	
tetrahydropyran-4-ylmethyl	ethyl	
tetrahydropyran-4-ylmethyl	*n*-propyl	
tetrahydropyran-4-ylmethyl	*n*-propyl	
tetrahydropyran-4-ylmethyl	*n*-propyl	
tetrahydropyran-4-ylmethyl	*n*-propyl	
tetrahydropyran-4-ylmethyl	*n*-propyl	
tetrahydropyran-4-ylmethyl	*n*-propyl	

tetrahydropyran-4-ylmethyl	methoxymethyl	
tetrahydropyran-4-ylmethyl	methoxymethyl	
tetrahydropyran-4-ylmethyl	methoxymethyl	
tetrahydropyran-4-ylmethyl	methoxymethyl	
tetrahydropyran-4-ylmethyl	methoxymethyl	
tetrahydropyran-4-ylmethyl	methoxymethyl	
tetrahydropyran-4-ylmethyl	ethoxymethyl	
tetrahydropyran-4-ylmethyl	ethoxymethyl	
tetrahydropyran-4-ylmethyl	ethoxymethyl	
tetrahydropyran-4-ylmethyl	ethoxymethyl	

tetrahydropyran-4-ylmethyl	ethoxymethyl	
tetrahydropyran-4-ylmethyl	ethoxymethyl	
tetrahydropyran-4-ylmethyl	2-methoxyethyl	
tetrahydropyran-4-ylmethyl	2-methoxyethyl	
tetrahydropyran-4-ylmethyl	2-methoxyethyl	
tetrahydropyran-4-ylmethyl	2-methoxyethyl	
tetrahydropyran-4-ylmethyl	2-methoxyethyl	
tetrahydropyran-4-ylmethyl	2-methoxyethyl	
tetrahydropyran-4-ylmethyl	hydroxymethyl	
tetrahydropyran-4-ylmethyl	hydroxymethyl	

tetrahydropyran-4-ylmethyl	hydroxymethyl	
tetrahydropyran-4-ylmethyl	hydroxymethyl	
tetrahydropyran-4-ylmethyl	hydroxymethyl	
tetrahydropyran-4-ylmethyl	hydroxymethyl	
tetrahydropyran-4-ylmethyl	2-hydroxyethyl	
tetrahydropyran-4-ylmethyl	2-hydroxyethyl	
tetrahydropyran-4-ylmethyl	2-hydroxyethyl	
tetrahydropyran-4-ylmethyl	2-hydroxyethyl	
tetrahydropyran-4-ylmethyl	2-hydroxyethyl	
tetrahydropyran-4-ylmethyl	2-hydroxyethyl	

Compounds of the invention have been found to modulate cytokine biosynthesis by inducing the production of interferon α and/or tumor necrosis factor α in human cells when tested using the methods described below.

CYTOKINE INDUCTION IN HUMAN CELLS

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon (α) and tumor necrosis factor (α) (IFN-α and TNF-α, respectively) secreted into culture media as described by Testerman et. al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", *Journal of Leukocyte Biology*, *58*, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). Alternately, whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at 4 x 10^6 cells/mL in RPMI complete. The PBMC suspension is added to 96 well flat bottom sterile tissue culture plates containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μM. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with reference compound.

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (usually 30-0.014 μM). The final concentration of PBMC suspension is 2 x 10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed and transferred to sterile polypropylene tubes. Samples are maintained at -30 to -70°C until analysis. The samples are analyzed for IFN-α by ELISA and for TNF-α by IGEN/BioVeris Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis

IFN-α concentration is determined with a human multi-subtype colorimetric sandwich ELISA (Catalog Number 41105) from PBL Biomedical Laboratories, Piscataway, NJ. Results are expressed in pg/mL.

The TNF-α concentration is determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from BioVeris Corporation, formerly known as IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF-α capture and detection antibody pair (Catalog Numbers AHC3419 and AHC3712) from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

Assay Data and Analysis

In total, the data output of the assay consists of concentration values of TNF-α and IFN-α (y-axis) as a function of compound concentration (x-axis).

Analysis of the data has two steps. First, the greater of the mean DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α) is subtracted from each reading. If any negative values result from background subtraction, the reading is reported as " * ", and is noted as not reliably

detectable. In subsequent calculations and statistics, " * ", is treated as a zero. Second, all background subtracted values are multiplied by a single adjustment ratio to decrease experiment to experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on the past 61 experiments (unadjusted readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the sum of the median dose values from the past 61 experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration (μmolar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α). The maximal response is the maximal amount of cytokine (pg/ml) produced in the dose-response.

CYTOKINE INDUCTION IN HUMAN CELLS (High Throughput Screen)

The CYTOKINE INDUCTION IN HUMAN CELLS test method described above was modified as follows for high throughput screening.

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at 4 x 10^6 cells/mL in RPMI complete (2-fold the final cell density). The PBMC suspension is added to 96-well flat bottom sterile tissue culture plates.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The compounds are generally tested at concentrations ranging from 30 - 0.014 μM. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with a reference compound 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1H-imidazo[4,5-c]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) on each plate. The solution of test compound is added at 7.5 mM to the first well of a dosing plate and serial 3 fold dilutions are made for the 7 subsequent concentrations in DMSO. RPMI Complete media is then added to the test compound dilutions in order to reach a final compound concentration of 2-fold higher (60 - 0.028 μM) than the final tested concentration range.

Incubation

Compound solution is then added to the wells containing the PBMC suspension bringing the test compound concentrations to the desired range (usually 30 - 0.014 μM) and the DMSO concentration to 0.4 %. The final concentration of PBMC suspension is $2x10^6$ cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 g) at 4°C. 4-plex Human Panel MSD MULTI-SPOT 96-well plates are pre-coated with the appropriate capture antibodies by MesoScale Discovery, Inc. (MSD, Gaithersburg, MD). The cell-free culture supernatants are removed and transferred to the MSD plates. Fresh samples are typically tested, although they may be maintained at -30 to -70°C until analysis.

Interferon-α and Tumor Necrosis Factor-α Analysis

MSD MULTI-SPOT plates contain within each well capture antibodies for human TNF-α and human IFN-α that have been pre-coated on specific spots. Each well contains four spots: one human TNF-α capture antibody (MSD) spot, one human IFN- α capture antibody (PBL Biomedical Laboratories, Piscataway, NJ) spot, and two inactive bovine

serum albumin spots. The human TNF-α capture and detection antibody pair is from MesoScale Discovery. The human IFN-α multi-subtype antibody (PBL Biomedical Laboratories) captures all IFN-α subtypes except IFN-α F (IFNA21). Standards consist of recombinant human TNF-α (R&D Systems, Minneapolis, MN) and IFN-α (PBL Biomedical Laboratories). Samples and separate standards are added at the time of analysis to each MSD plate. Two human IFN-α detection antibodies (Cat. Nos. 21112 & 21100, PBL) are used in a two to one ratio (weight:weight) to each other to determine the IFN-α concentrations. The cytokine-specific detection antibodies are labeled with the SULFO-TAG reagent (MSD). After adding the SULFO-TAG labeled detection antibodies to the wells, each well's electrochemoluminescent levels are read using MSD's SECTOR HTS READER. Results are expressed in pg/mL upon calculation with known cytokine standards.

Assay Data and Analysis

In total, the data output of the assay consists of concentration values of TNF-α or IFN-α (y-axis) as a function of compound concentration (x-axis).

A plate-wise scaling is performed within a given experiment aimed at reducing plate-to-plate variability associated within the same experiment. First, the greater of the median DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α) is subtracted from each reading. Negative values that may result from background subtraction are set to zero. Each plate within a given experiment has a reference compound that serves as a control. This control is used to calculate a median expected area under the curve across all plates in the assay. A plate-wise scaling factor is calculated for each plate as a ratio of the area of the reference compound on the particular plate to the median expected area for the entire experiment. The data from each plate are then multiplied by the plate-wise scaling factor for all plates. Only data from plates bearing a scaling factor of between 0.5 and 2.0 (for both cytokines IFN-α, TNF-α) are reported. Data from plates with scaling factors outside the above mentioned interval are retested until they bear scaling factors inside the above mentioned interval. The above method produces a scaling of the y-values without altering the shape of the curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No.

5,352,784; Example 91). The median expected area is the median area across all plates that are part of a given experiment.

A second scaling may also be performed to reduce inter-experiment variability (across multiple experiments). All background-subtracted values are multiplied by a single adjustment ratio to decrease experiment-to-experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on an average of previous experiments (unadjusted readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the sum of the median dose values from an average of previous experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration (μmolar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α). The maximal response is the maximal amount of cytokine (pg/ml) produced in the dose-response.

TNF-α INHIBITION IN MOUSE CELLS

Certain compounds of the invention may modulate cytokine biosynthesis by inhibiting production of tumor necrosis factor α (TNF-α) when tested using the method described below.

The mouse macrophage cell line Raw 264.7 is used to assess the ability of compounds to inhibit tumor necrosis factor-α (TNF-α) production upon stimulation by lipopolysaccharide (LPS).

Single Concentration Assay:

Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 3 x 10^5 cells/mL in RPMI with 10 % fetal bovine serum (FBS). Cell suspension (100 μL) is added to 96-well flat bottom sterile tissues culture plates

(Becton Dickinson Labware, Lincoln Park, NJ). The final concentration of cells is 3 x 10^4 cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 5μM. LPS (Lipopolysaccaride from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC_{70} concentration as measured by a dose response assay.

Incubation

A solution of test compound (1μl) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (1 μL, EC_{70} concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

TNF-α Analysis

Following the incubation the supernatant is removed with a pipet. TNF-α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource International, Camarillo, CA). Results are expressed in pg/mL. TNF-α expression upon LPS stimulation alone is considered a 100% response.

Dose Response Assay:

Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 4 x 10^5 cells/mL in RPMI with 10 % FBS. Cell suspension (250 μL) is added to 48-well flat bottom sterile tissues culture plates (Costar, Cambridge, MA). The final concentration of cells is 1 x 10^5 cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 0.03, 0.1, 0.3, 1, 3, 5 and 10 μM. LPS (Lipopolysaccaride from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC_{70} concentration as measured by dose response assay.

Incubation

A solution of test compound (200 μl) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (200 μL, EC_{70} concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

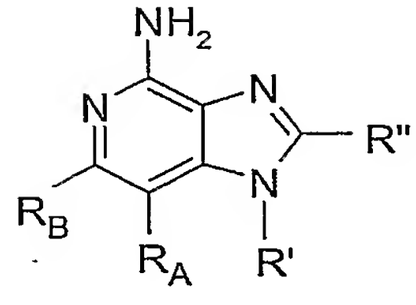
TNF-α Analysis

Following the incubation the supernatant is removed with a pipet. TNF-α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource International, Camarillo, CA). Results are expressed in pg/mL. TNF-α expression upon LPS stimulation alone is considered a 100% response.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

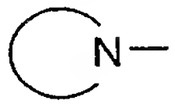
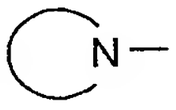
WHAT IS CLAIMED IS:

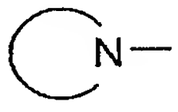
1. A compound of formula (I):



I

wherein:

R_A and R_B taken together form a fused benzene ring or fused pyridine ring wherein the benzene ring or pyridine ring is substituted by one  group, or substituted by one  group and one R group;

 is a heterocyclic ring system wherein the ring containing the nitrogen atom bonded to the imidazoquinoline or imidazonaphthyridine radical of the compound of Formula I is unsaturated or partially saturated, and wherein the heterocyclic ring system is mono-, bi-, or tricyclic, and can contain 4 to 14 ring atoms, up to 2 of which, in addition to the nitrogen atom bonded to the imidazoquinoline or imidazonaphthyridine radical, are optionally a heteroatom selected from N, O, and S, and wherein the heterocyclic ring system is unsubstituted or substituted by one or more substituents selected from the group consisting of:

alkoxy,

alkylenedioxy,

hydroxy,

nitro,

oxo,

thioxo,

$-R_4$,

$-Y-R_4$,

-X-Y-R_4,

=N-Q-R_4,

=N-CN, and

=N-OH;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

-O-C(O)-O-,

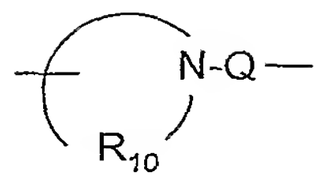
-O-$S(O)_2$-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

-$C(R_6)$-$N(OR_9)$-,



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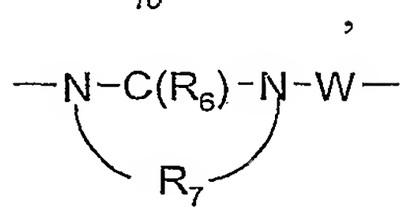

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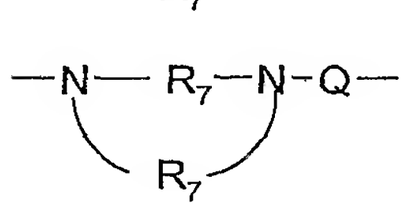

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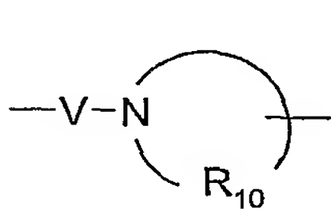

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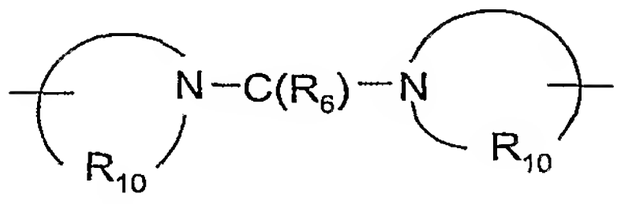


;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, and -C(R_6)-N(OR_9)-;

V is selected from the group consisting of a bond, -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

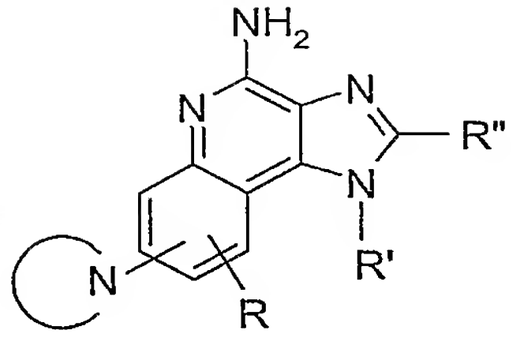
R_{10} is C_{3-8} alkylene;

R is selected from the group consisting of hydrogen, alkyl, alkoxy, trifluoromethyl, chloro, fluoro, and hydroxy; and

R' and R" are independently selected from the group consisting of hydrogen and non-interfering substituents;

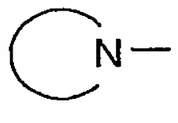
or a pharmaceutically acceptable salt thereof.

2. A compound of formula (II):



II

wherein:



is a heterocyclic ring system wherein the ring containing the nitrogen atom bonded to the imidazoquinoline radical of the compound of Formula II is unsaturated or partially saturated, and wherein the heterocyclic ring system is mono-, bi-, or tricyclic, and can contain 4 to 14 ring atoms, up to 2 of which, in addition to the nitrogen atom bonded to the imidazoquinoline radical, are optionally a heteroatom selected from N, O, and S, and wherein the heterocyclic ring system is unsubstituted or substituted by one or more substituents selected from the group consisting of:

alkoxy,

alkylenedioxy,

hydroxy,

nitro,

oxo,

thioxo,

$-R_4$,

$-Y-R_4$,

$-X-Y-R_4$,

$=N-Q-R_4$,

=N-CN, and

=N-OH;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl,

and heterocyclylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

-O-C(O)-O-,

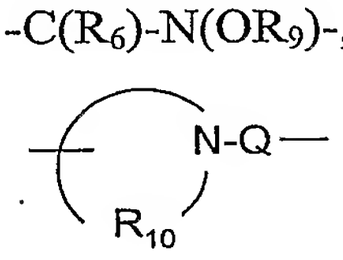
$-O-S(O)_2-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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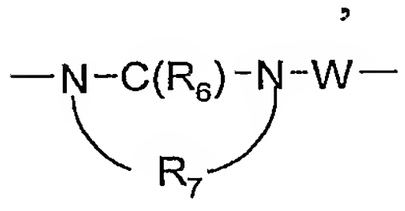

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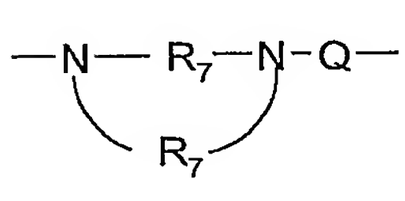

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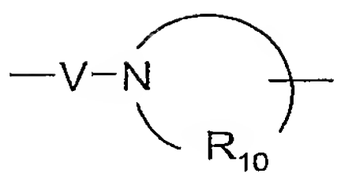
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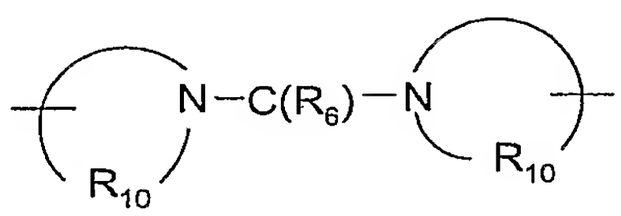

;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, and -C(R_6)-N(OR_9)-;

V is selected from the group consisting of a bond, -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and \-S(O)$_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

R is selected from the group consisting of hydrogen, alkyl, alkoxy, trifluoromethyl, chloro, fluoro, and hydroxy; and

R' and R" are independently selected from the group consisting of hydrogen and non-interfering substituents;

or a pharmaceutically acceptable salt thereof.

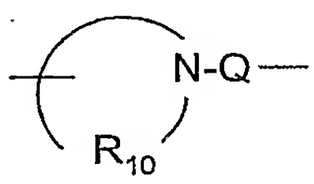
3. The compound or salt of claim 2 wherein:

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy,

heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

Y is selected from the group consisting of $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-O-S(O)_2-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$,



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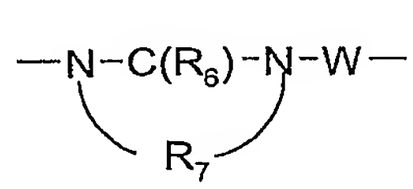

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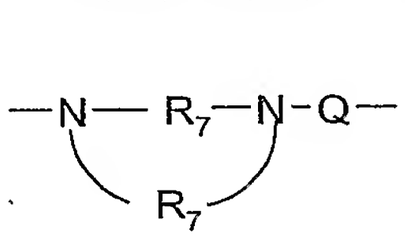

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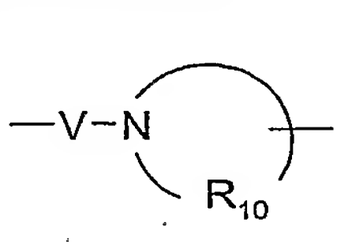

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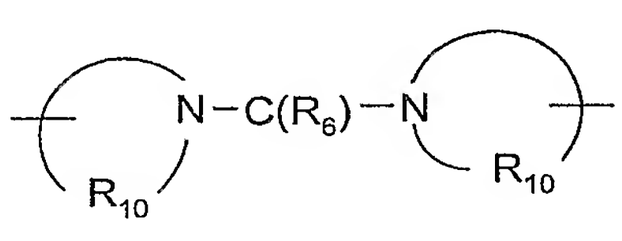

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4. The compound or salt of claim 1 or 2 wherein R' is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

-O-C(O)-O-,

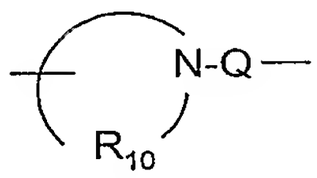
-O-S(O)$_2$-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

-C(R_6)-N(OR_9)-,



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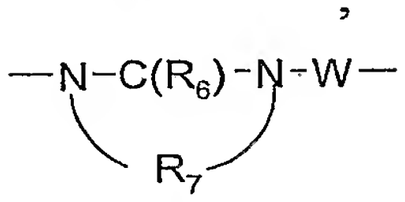

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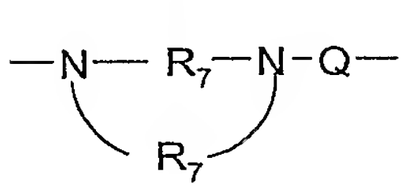

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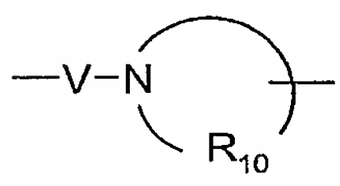

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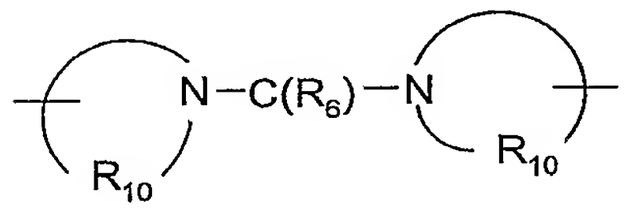
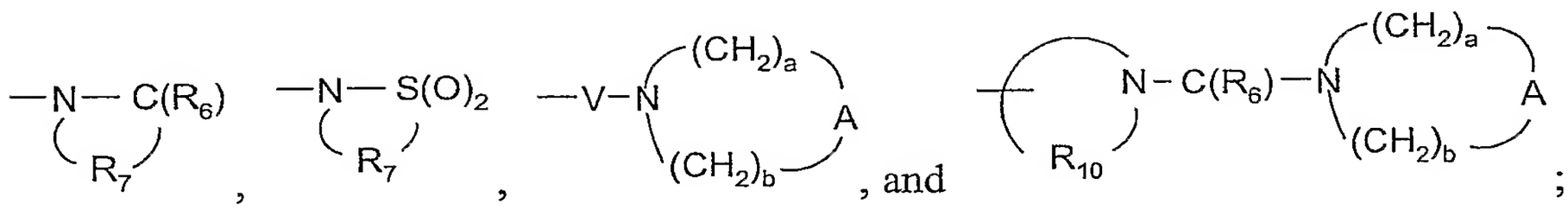


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}$-, $-CH_2$-, and $-N(R_4)$-;

Q is selected from the group consisting of a bond, $-C(R_6)$-, $-C(R_6)-C(R_6)$-, $-S(O)_2$-, $-C(R_6)-N(R_8)-W$-, $-S(O)_2-N(R_8)$-, $-C(R_6)-O$-, and $-C(R_6)-N(OR_9)$-;

V is selected from the group consisting of a bond, $-C(R_6)$-, $-O-C(R_6)$-, $-N(R_8)-C(R_6)$-, and $-S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

5. The compound or salt of claim 1 or 2 wherein R" is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}$-,

$-S(O)_2-N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

-O-C(O)-O-,

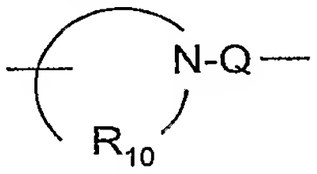
-O-$S(O)_2$-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

-$C(R_6)$-$N(OR_9)$-,



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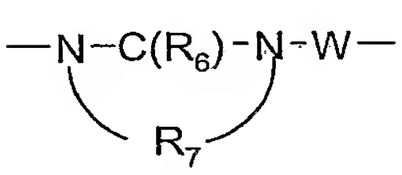

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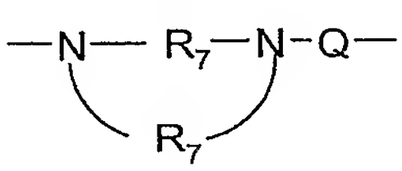

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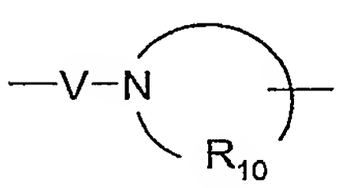

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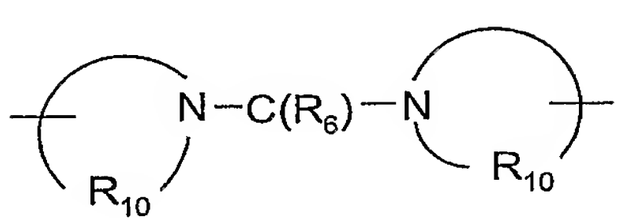
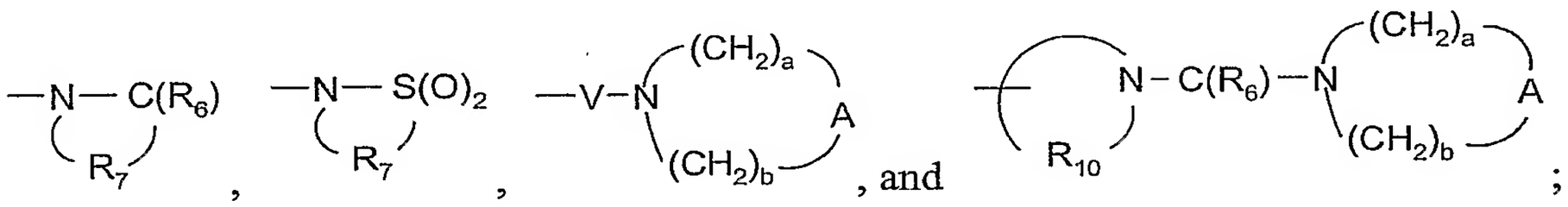


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl,

amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}$-, $-CH_2$-, and $-N(R_4)$-;

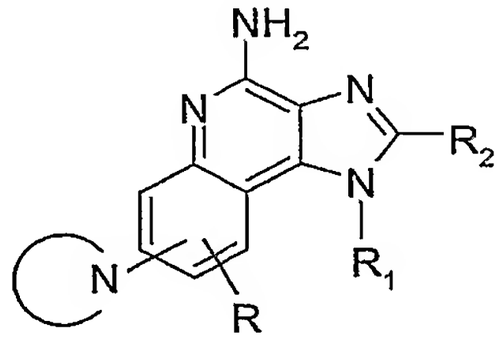
Q is selected from the group consisting of a bond, $-C(R_6)$-, $-C(R_6)-C(R_6)$-, $-S(O)_2$-, $-C(R_6)-N(R_8)-W$-, $-S(O)_2-N(R_8)$-, $-C(R_6)-O$-, and $-C(R_6)-N(OR_9)$-;

V is selected from the group consisting of a bond, $-C(R_6)$-, $-O-C(R_6)$-, $-N(R_8)-C(R_6)$-, and $-S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-; and

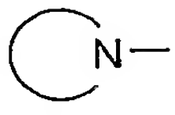
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

6. A compound of formula (IIa):



IIa

wherein:

 is a heterocyclic ring system wherein the ring containing the nitrogen atom bonded to the imidazoquinoline radical of the compound of Formula I is unsaturated or partially saturated, and wherein the heterocyclic ring system is mono-, bi-, or tricyclic,

and can contain 4 to 14 ring atoms, up to 2 of which, in addition to the nitrogen atom bonded to the imidazoquinoline radical, are optionally a heteroatom selected from N, O, and S, and wherein the heterocyclic ring system is unsubstituted or substituted by one or more substituents selected from the group consisting of:

alkoxy,

alkylenedioxy,

hydroxy,

nitro,

oxo,

thioxo,

$-R_4$,

$-Y-R_4$,

$-X-Y-R_4$,

$=N-Q-R_4$,

=N-CN, and

=N-OH;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

-O-C(O)-O-,

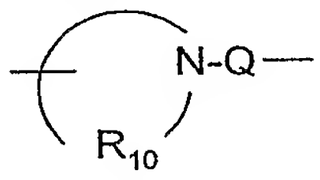
$-O-S(O)_2-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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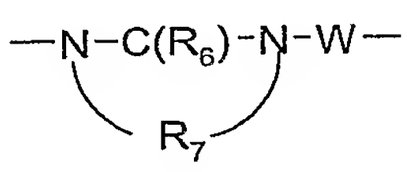

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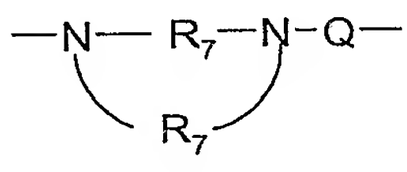

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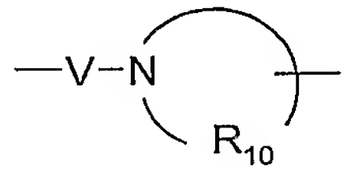

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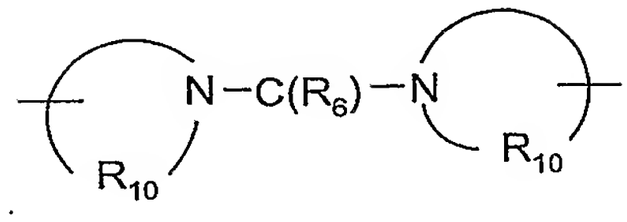
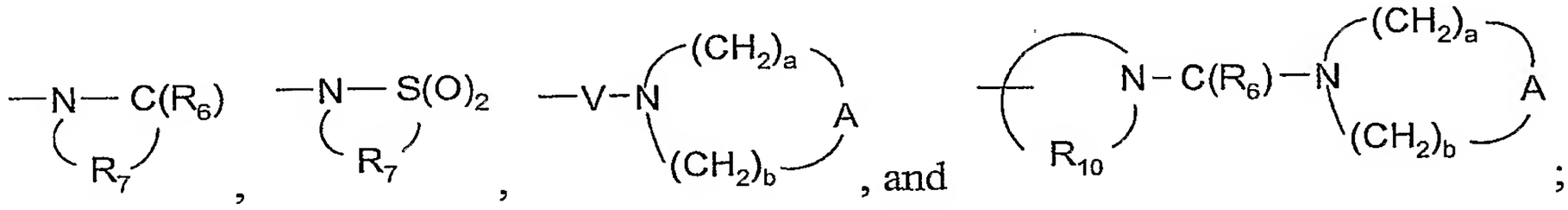


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy,

hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

A is selected from the group consisting of -O-, -C(O)-, -$S(O)_{0-2}$-, -CH_2-, and -$N(R_4)$-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, and -$C(R_6)$-$N(OR_9)$-;

V is selected from the group consisting of a bond, -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-;

each a and each b is independently an integer from 1 to 6 with the proviso that a + b in each ring is ≤ 7;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene; and

R is selected from the group consisting of hydrogen, alkyl, alkoxy, trifluoromethyl, chloro, fluoro, and hydroxy;

or a pharmaceutically acceptable salt thereof.

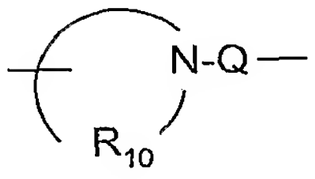
7. The compound or salt of claim 6 wherein:

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,

heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

Y is selected from the group consisting of $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-O-S(O)_2-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$,



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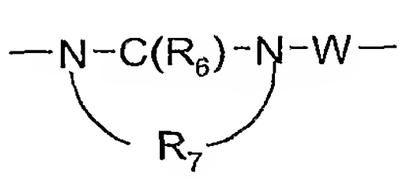

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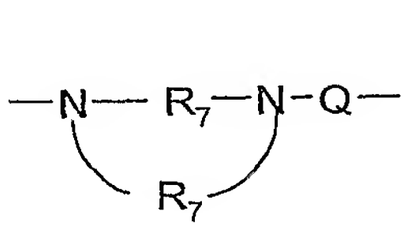

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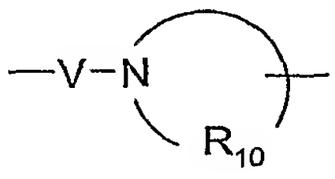

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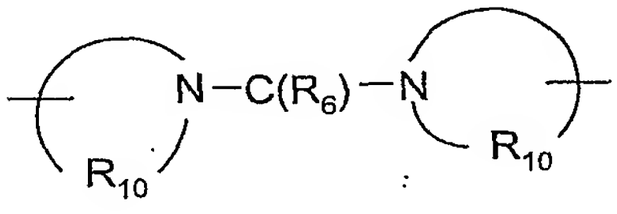

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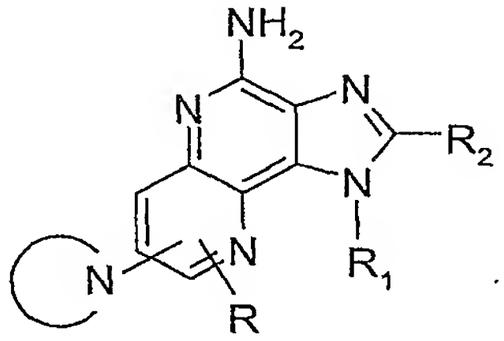
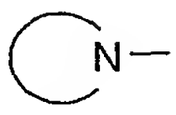
8. A compound of formula (III):



III

wherein:



is a heterocyclic ring system wherein the ring containing the nitrogen atom bonded to the imidazonaphthyridine radical of the compound of Formula I is unsaturated or partially saturated, and wherein the heterocyclic ring system is mono-, bi-, or tricyclic, and can contain 4 to 14 ring atoms, up to 2 of which, in addition to the nitrogen atom bonded to the imidazonaphthyridine radical, are optionally a heteroatom

selected from N, O, and S, and wherein the heterocyclic ring system is unsubstituted or substituted by one or more substituents selected from the group consisting of:

alkoxy,

alkylenedioxy,

hydroxy,

nitro,

oxo,

thioxo,

$-R_4$,

$-Y-R_4$,

$-X-Y-R_4$,

$=N-Q-R_4$,

=N-CN, and

=N-OH;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

$-O-C(O)-O-$,

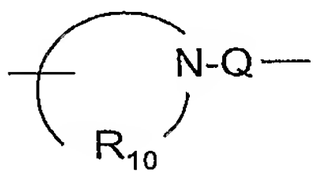
$-O-S(O)_2-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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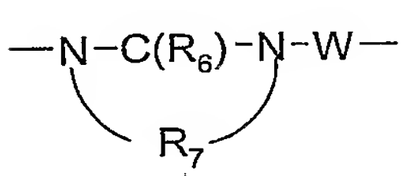

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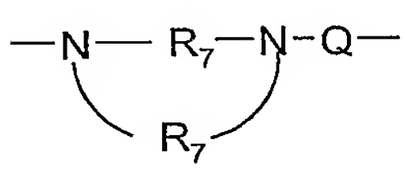

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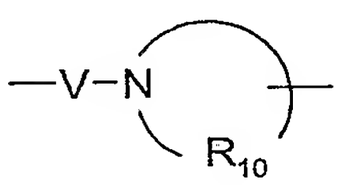

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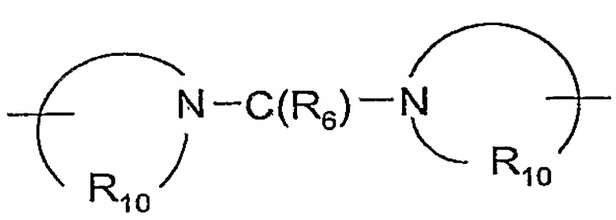
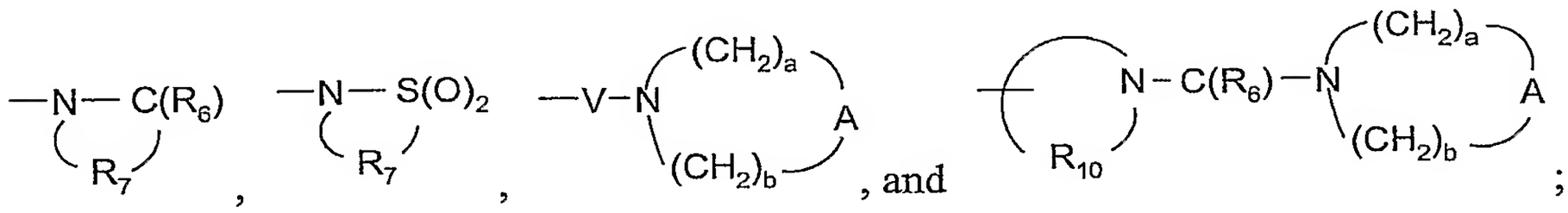


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl,

amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

A is selected from the group consisting of -O-, -C(O)-, -$S(O)_{0-2}$-, -CH_2-, and -$N(R_4)$-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, and -$C(R_6)$-$N(OR_9)$-;

V is selected from the group consisting of a bond, -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-;

each a and each b is independently an integer from 1 to 6 with the proviso that a + b in each ring is ≤ 7;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

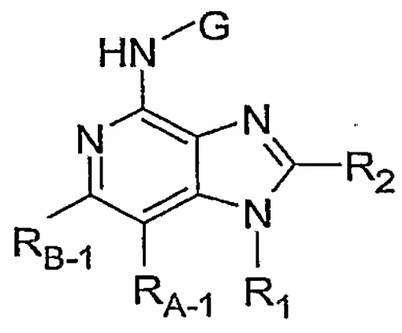
R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene; and

R is selected from the group consisting of hydrogen, alkyl, alkoxy, trifluoromethyl, chloro, fluoro, and hydroxy;

or a pharmaceutically acceptable salt thereof.

9. A compound of the Formula (IV):



IV

wherein:

G is selected from the group consisting of:

-C(O)-R'",

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

-C(O)-O-R'",

-C(O)-N(R'"")R'",

-C(=NY')-R'",

-CH(OH)-C(O)-OY',

-CH(OC_{1-4} alkyl)Y_0,

-CH_2Y_1, and

-$CH(CH_3)Y_1$;

R'" and R'"" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, and benzyl, each of which may be unsubstituted or substituted by one or more substitutents selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, arylC_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl, haloC_{1-4} alkylenyl, haloC_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2, with the proviso that R'"" can also be hydrogen;

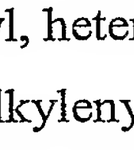
α-aminoacyl is an acyl group derived from an amino acid selected from the group consisting of racemic, D-, and L-amino acids;

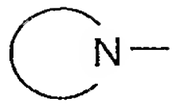
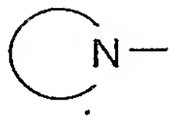
Y' is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl;

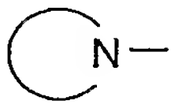
Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxyC_{1-6} alkylenyl, aminoC_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylaminoC_{1-4} alkylenyl, and di-*N,N*-C_{1-6} alkylaminoC_{1-4} alkylenyl;

Y_1 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl;

R_{A-1} and R_{B-1} taken together form a fused benzene ring or fused pyridine ring

wherein the fused pyridine ring is  wherein the highlighted bond indicates the position where the ring is fused, and wherein the benzene ring or pyridine ring is

substituted by one  group, or substituted by one  group and one R group;

 is a heterocyclic ring system wherein the ring containing the nitrogen atom bonded to the imidazoquinoline radical of the compound of Formula I is unsaturated or partially saturated, and wherein the heterocyclic ring system is mono-, bi-, or tricyclic, and can contain 4 to 14 ring atoms, up to 2 of which, in addition to the nitrogen atom bonded to the imidazoquinoline radical, are optionally a heteroatom selected from N, O, and S, and wherein the heterocyclic ring system is unsubstituted or substituted by one or more substituents selected from the group consisting of:

alkoxy,

alkylenedioxy,

hydroxy,

nitro,

oxo,

thioxo,

$-R_4$,

$-Y-R_4$,

$-X-Y-R_4$,

$=N-Q-R_4$,

=N-CN, and

=N-OH;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

-X-R_5;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

-O-C(O)-O-,

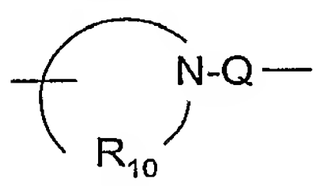
-O-$S(O)_2$-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

-$C(R_6)$-$N(OR_9)$-,



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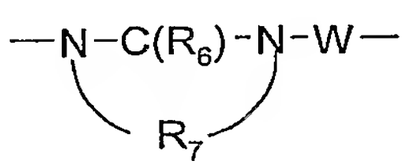

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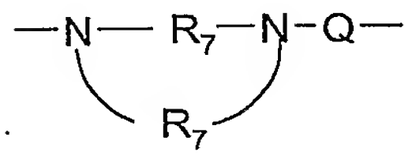
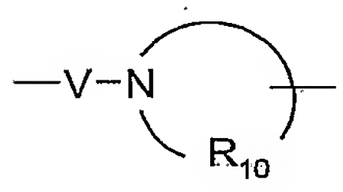
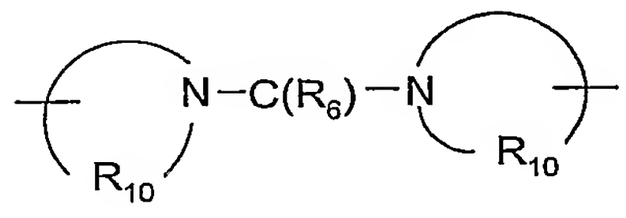


,



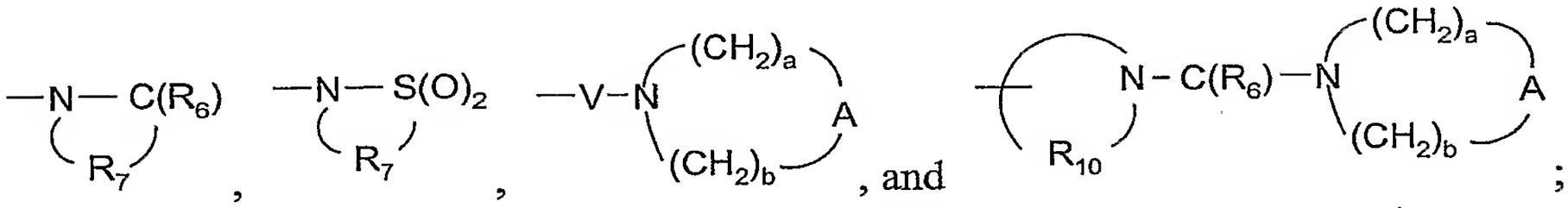
, and



;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, heterocyclyl, and heterocyclylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

A is selected from the group consisting of -O-, -C(O)-, -$S(O)_{0-2}$-, -CH_2-, and -$N(R_4)$-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, and -$C(R_6)$-$N(OR_9)$-;

V is selected from the group consisting of a bond, -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-;

each a and each b is independently an integer from 1 to 6 with the proviso that a + b in each ring is ≤ 7;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

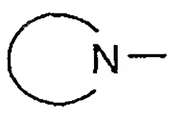
R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

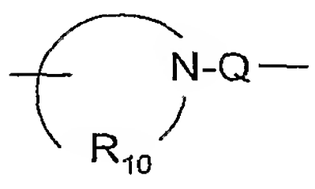
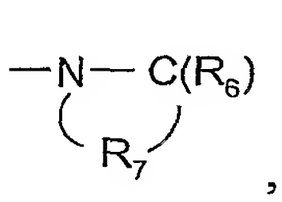
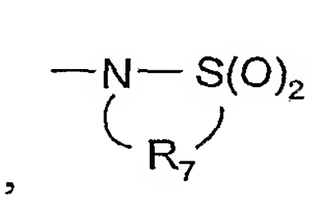
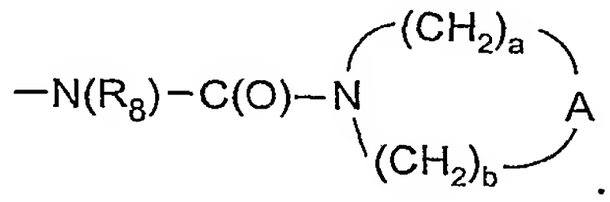
R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene; and

R is selected from the group consisting of hydrogen, alkyl, alkoxy, trifluoromethyl, chloro, fluoro, and hydroxy;

or a pharmaceutically acceptable salt thereof.

10. The compound or salt of claim 2, 3, 4 as dependent on claim 2, 5 as dependent on claim 2, 6, 7, 8 or 9 wherein  is attached at the 7 position.

11. The compound or salt of claim 6, 7, 8, 9, or 10 as dependent on claim 6, 7, 8 or 9 wherein R_1 is selected from the group consisting of alkyl, hydroxyalkyl, alkoxyalkylenyl, arylalkylenyl, aryloxyalkylenyl, heterocyclylalkylenyl, -X-Y-R_4, and -X-R_5; wherein X is alkylene; Y is selected from the group consisting of -$S(O)_{0-2}$-, -$N(R_8)$-Q-, and  ; R_4 is selected from the group consisting of alkyl, aryl, and heteroaryl; and R_5 is selected from the group consisting of  ,  , and  .

12. The compound or salt of claim 11 wherein R_1 is selected from the group consisting of alkyl, hydroxyalkyl, alkoxyalkylenyl, and heterocyclylalkylenyl.

13. The compound or salt of claim 12 wherein R_1 is selected from the group consisting of propyl, 2-methylpropyl, 2-hydroxy-2-methylpropyl, 2,3-dihydroxypropyl, 3-isopropoxypropyl, and tetrahydropyran-4-ylmethyl.

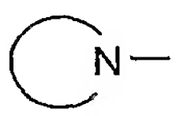
14. The compound or salt of claim 6, 7, 8, 9, 10 as dependent on claim 6, 7, 8 or 9, 11, 12, or 13 wherein R_2 is R_4.

15. The compound or salt of claim 14 wherein R_2 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and hydroxyalkylenyl.

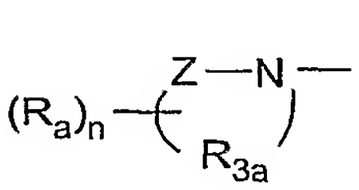
16. The compound or salt of claim 15 wherein R_2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-4} alkyl-O-C_{1-4} alkylenyl, and HO-C_{1-4} alkylenyl.

17. The compound or salt of claim 16 wherein R_2 is selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *n*-butyl, ethoxymethyl, methoxymethyl, 2-methoxyethyl, hydroxymethyl, and 2-hydroxyethyl.

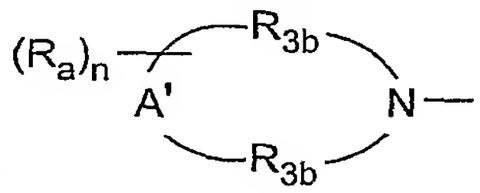
18. The compound or salt of any one of claims 1 through 17 wherein



is selected from the group consisting of:



and



;

wherein:

Z is selected from the group consisting of -C(O)-, -C(S)-, -$S(O)_{0-2}$-, -OC(O)-, -N(Q-R_4)-C(O)-, -N(Q-R_4)-C(S)-, and -N(Q-R_4)-$S(O)_2$-;

R_{3a} is C_{2-7} alkylene;

A' is selected from the group consisting of -O-, -C(O)-, -CH_2-, -$S(O)_{0-2}$-, -N(Q-R_4)-, and -C(O)-N(Q-R_4)-;

R_{3b} is C_{1-5} alkylene wherein both R_{3b} groups combined have a total of up to seven carbon atoms;

R_a is selected from the group consisting of:

alkoxy,

alkylenedioxy,

hydroxy,

nitro,

oxo,

thioxo,

-R_4,

-Y-R_4,

-X-Y-R_4,

=N-Q-R_4,

=N-CN, and

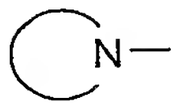
=N-OH; and

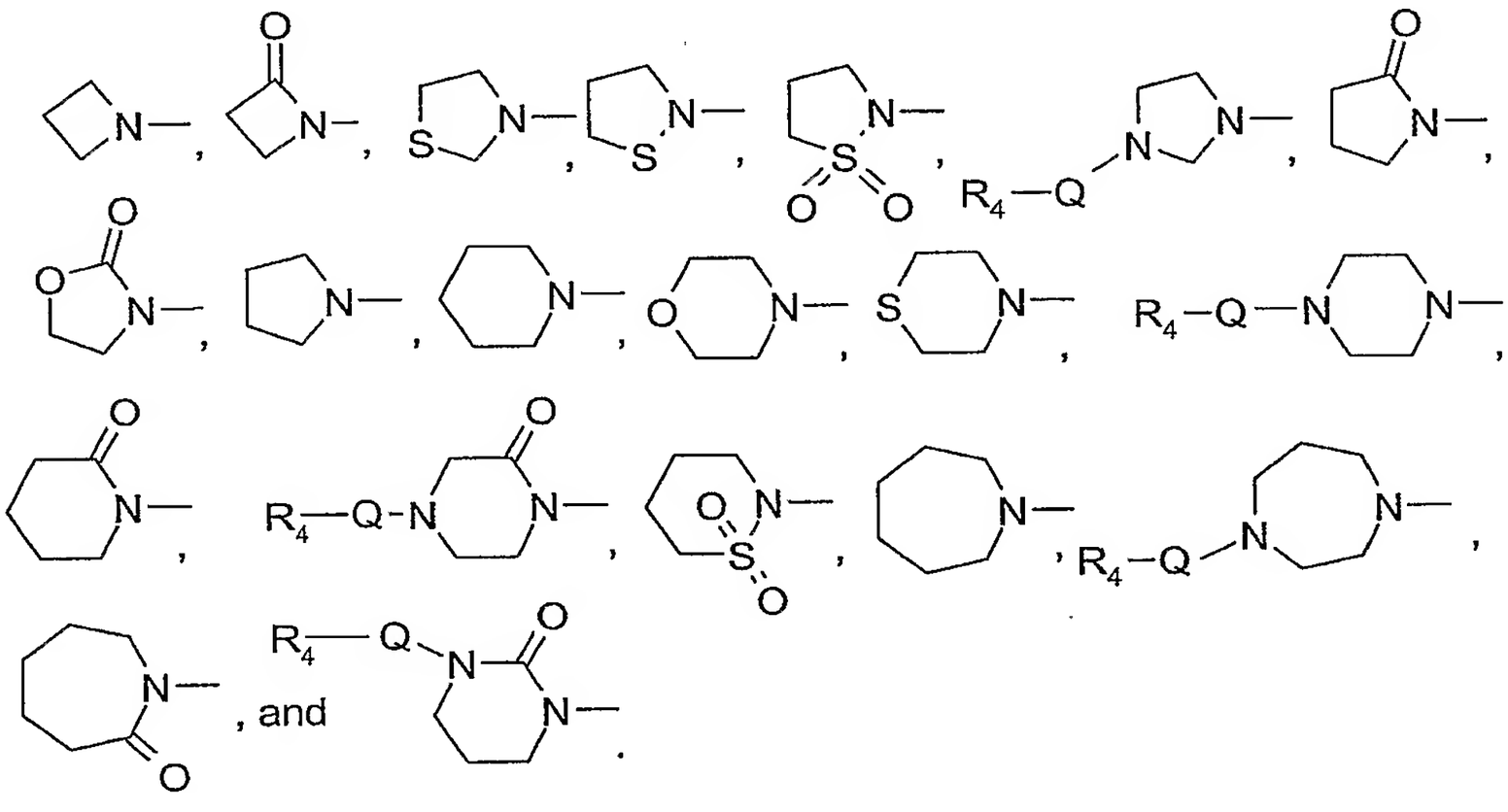
n is 0 or 1.

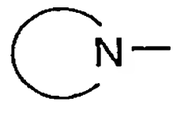
19. The compound or salt of claim 18 wherein R_a is hydroxy, alkoxy, oxo, or R_4.

20. The compound or salt of claim 18 wherein n is 0.

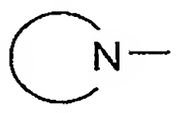
21. The compound or salt of claim 18 wherein

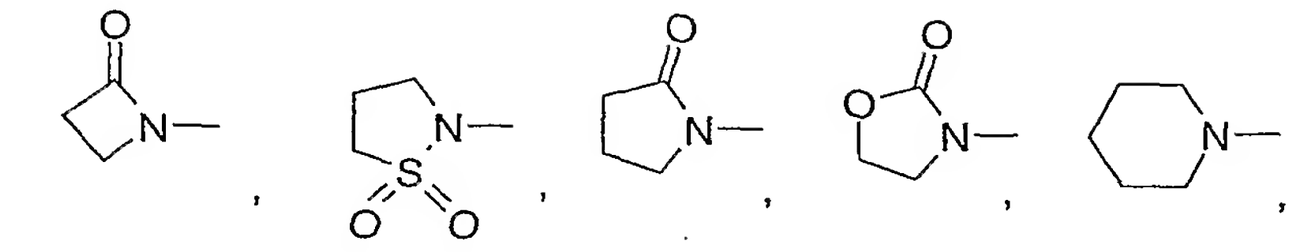
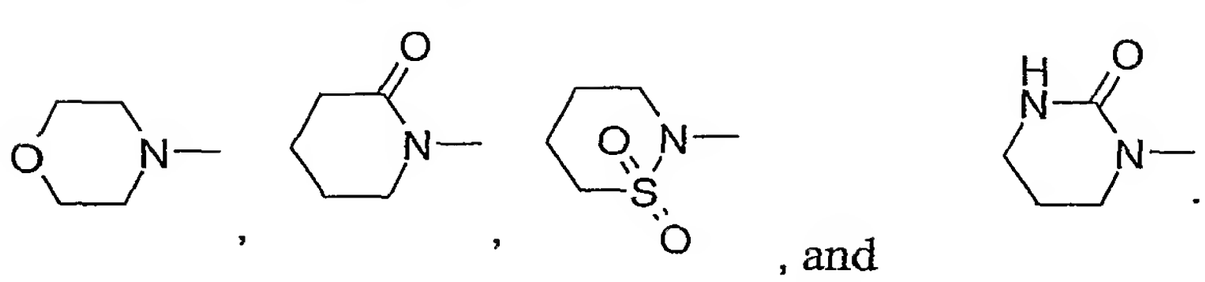

is selected from the group consisting of:



22. The compound or salt of claim 21 wherein R_4-Q- in  is selected from the group consisting of hydrogen, alkyl, acyl, alkylsulfonyl, and arylsulfonyl.

23. The compound or salt of claim 21 wherein


is selected from the group consisting of:



, and

24. The compound or salt of any one of claims 1 through 23 wherein R is hydrogen.

25. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of claims 1 through 24 and a pharmaceutically acceptable carrier.

26. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of any one of claims 1 through 24 or a pharmaceutical composition of claim 25 to the animal.

27. A method of treating a viral disease in an animal comprising administering an effective amount of a compound or salt of any one of claims 1 through 24 or a pharmaceutical composition of claim 25 to the animal.

28. A method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt of any one of claims 1 through 24 or a pharmaceutical composition of claim 25 to the animal.